

CUL2 H06330-19 - p25885

BRITISH JOURNAL OF UROLOGY

Journal of the
British Association of Urological Surgeons

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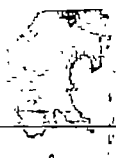
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P 25 885

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British Journal of Urology

Volume 65



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REVIEW

The Dangers of a Long Urological Waiting List

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It is not at all clear why a new specialty will rapidly generate enough clinical material to establish its own *raison d'être*. It seems incomprehensible to senior clinicians, who in the past successfully and often single-handedly managed the various ills of a stable population, that their proliferating junior colleagues in the sub-specialties derived from a more general practice are unable to cope with exploding NHS waiting lists. The standard of care for patients presenting earlier may have improved though they must wait longer to receive it (Frankel, 1989).

Waiting lists serve several important purposes. Many naively but often successfully use it as a status symbol and a weapon to obtain more manpower and resources and to demonstrate that their clinical contribution to the community is indispensable. On the contrary, short lists can indicate an efficient and hard-working management policy to control the clinical workload.

A more important function of the waiting list is the rationing of demand for a scarce commodity. Enoch Powell has succinctly explained the necessity of generating delay to maintain a steady flow of cases. This state of affairs contrasts with that in the private sector, where time wasted in out-patient clinics and on incompletely filled operating lists is paid for by the patients (Garner, 1979).

Despite the shrill denunciation of Government policies, it is doubtful if the NHS could ever function without waiting lists. There may even be some benefit in maintaining them. Patients often die (on whom expensive treatment would have been wasted) and some will have second thoughts. Others will emigrate or lose patience and join a private health care scheme, thus saving the NHS the cost of their treatment. A relatively high proportion of

patients default on their appointments for out-patient clinics or in-patient admission, indicating perhaps a natural remission or tolerance of symptoms. Furthermore, whilst a patient resides on a waiting list, better methods of objective assessment resulting in a more accurate diagnosis and new medications may be introduced which reduce the indications for surgery.

Remedies to reduce the waiting list are often introduced as a package at a politically sensitive time and include provision of extra operating facilities, introduction of day case surgery where none existed before, redeployment of manpower and financial initiatives. It seems doubtful if these have any permanent effect and they could lead to unnecessary surgery being performed.

The significance of waiting time/numbers on the list—a major deception?

It is clear that waiting list statistics are misleading (Lancet, 1981a). The standard DHSS form SBH 203 excludes day cases, patients who fail to accept an admission date or for whom admission is deferred on medical or social grounds, and planned review cases (*e.g.* check cystoscopy). Indeed there are many other priorities on the use of a surgical bed and/or a space on an operating list not accounted for by a simple list of projected elective admissions. A managing authority might see a surgeon's work only in terms of his official waiting list when in fact his true list, taking account of the other components, may be 80% greater (Table). There is also a need to categorise patients on a waiting list in a standard form based on particular diagnoses or even on a basis of projected in-patient bed day times (Sanderson, 1982; Morris, 1984; Sykes, 1986).

The waiting lists for surgical treatment show a high degree of regional variation which has never

Table Potential Occupants of a Surgical Bed and/or Position on an Operating List (after Sykes, 1986)

1. Emergency admission through "Accident and Emergency"
2. Emergency admission through G.P. referral
3. Emergency admission through consultant referral (secondary and tertiary)
4. Transfer from medical ward
5. Planned day case
6. Review case, e.g. check cystoscopy
7. Planned admission—deferred (a) for medical reasons (b) failed to attend
8. Planned elective admission, on waiting list

Categories 1–7 not accounted in waiting list statistics.

been wholly explained (Figs 1 and 2) (Timmins, 1985). It must relate in some degree to efficiency in balancing out-patient numbers with availability of beds, surgeons' experience, adequate staffing of operating theatres and varying periods of post-operative in-patient admission which, even for

standard procedures, can differ according to the whims of the consultant in charge (Lancet, 1981b; Owen, 1976). The evaluation of data on in-patient and out-patient waiting times is complicated by the fact that different policies may operate. There tends to be an inverse correlation between the two, although both are usually very long.

In Figures 1 and 2 the variation in numbers of patients on urology waiting lists by region is shown for the month of September 1987, a period chosen at random from DHSS statistics. The difference between the least and the greatest differs by a factor of 6. There is also considerable variation in the proportion of patients regarded as urgent. In Figure 3 the total number of patients on waiting lists is plotted against the death rates from bladder cancer. It may be of interest that this tends to show a trend in their association. Almost certainly this impression is pejorative and the solution is merely that regions more sparsely populated with respect to patients with bladder cancer will naturally have fewer deaths.

Some of the variation between units may relate to differing criteria for enlistment. This has been explored in detail by Sanderson (1982) and is now worth reviewing. In Figure 4 the natural progression of a disease is depicted graphically. "A" represents the point at which treatment is unequivocally required and for which the patient is admitted. The

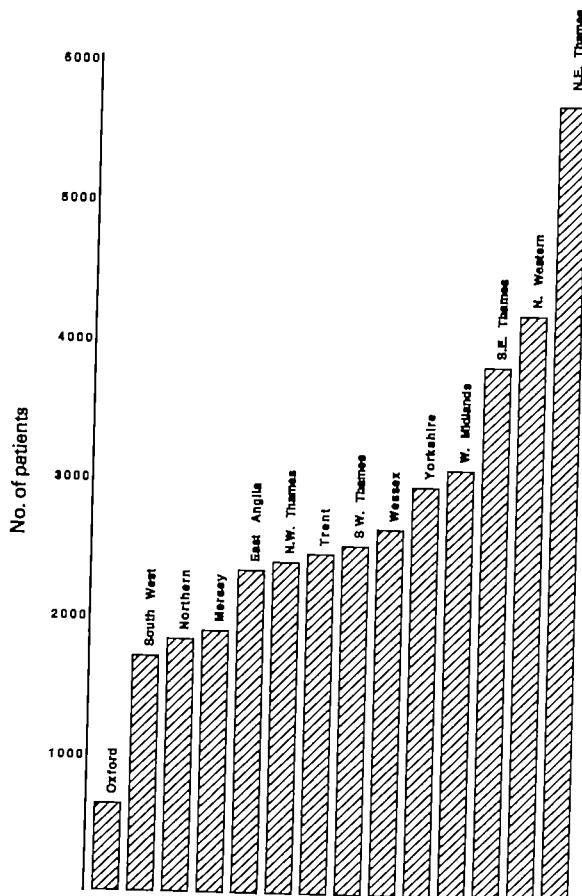


Fig. 1 Number of patients on urology waiting lists, by region, in September 1987.

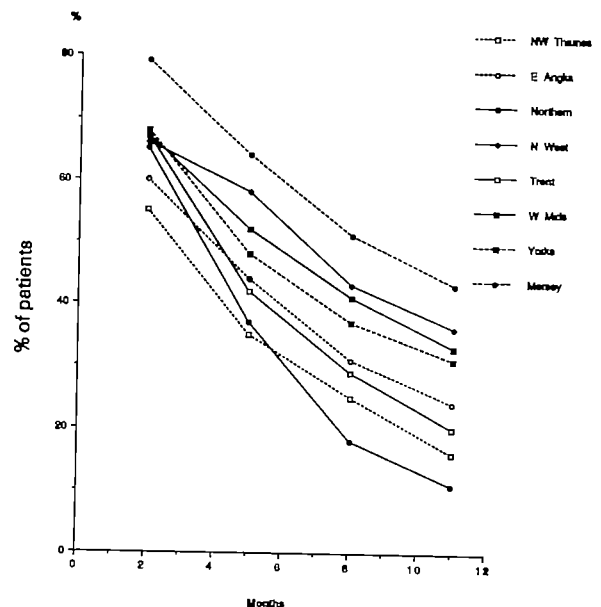


Fig. 2 Percentage of patients waiting (in months) in a sample of regions shown in Figure 1.

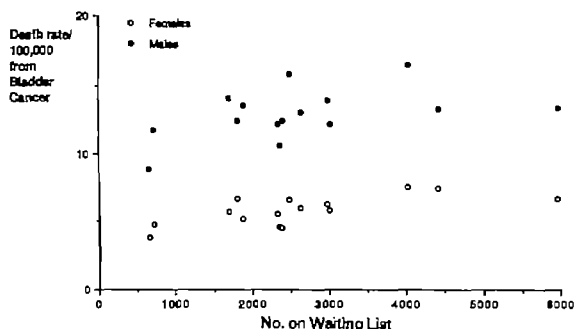


Fig. 3 Death rate per 100,000 population versus total number on urology departments' waiting lists.

surgeon will attempt to predict this in the out-patient clinic and put the patient on the list (at point "W") in time to avoid irreversible morbidity and to minimise discomfort. Ideally, a disease should progress at a regular rate and be constantly monitored so that "W" and "A" are close and therefore a waiting list comprises patients definitely requiring surgical treatment in the near future. Unfortunately, the rate of progression of most diseases and the threshold of severity of "W" are highly variable functions. An example is quoted of the different waiting list management policies operated by two ophthalmologists in the treatment of patients presenting with cataracts. The first consultant saw patients only once after referral by the family doctor; assuming that the condition would progress at a steady rate, he put the patients on the waiting list immediately. The second consultant reviewed patients regularly but enlisted them only when there was evidence of diminishing

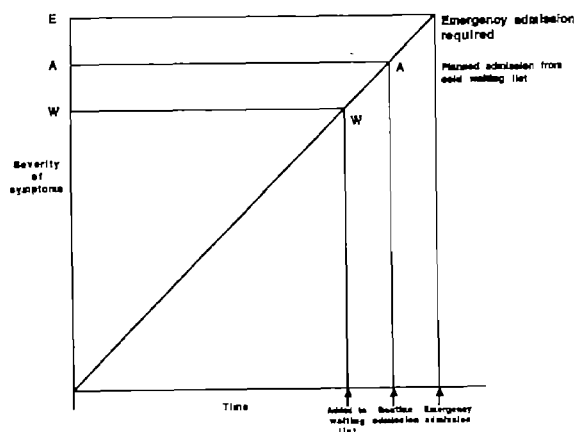


Fig. 4 Symptomatic threshold versus time on waiting list. Preferably TA should be fixed on the linear progression of symptoms, not far from TW but well below TE.

visual acuity. The first surgeon obviously had a longer waiting list than the second. However, there was no difference in the visual disability ultimately displayed in both groups on admission. In urology it is likely that similar phenomena could be demonstrated (e.g. the management of prostaticism).

The causes of diagnostic delay

Whilst the dangers of delay in management of many conditions may be extraordinarily difficult to establish, there is no doubt that for some individuals delay can threaten their chances of survival. The period between presentation and definitive management may derive from the time taken by the patient to report his symptoms to the General Practitioner, the duration of G.P. management, delay in obtaining an appointment after referral to a specialist clinic and further delay before the second appointment to discuss the results of investigations. The total of these components must therefore be added to waiting list time for operative treatment.

Limiting delay before hospital referral is a matter of public education and, in particular, for the early diagnosis of malignant disease, establishment of screening programmes. Delay on the part of the G.P. is decreasing with rising standards of medical care, but examples of classic errors are still encountered: testicular tumours are misdiagnosed, torsion is attributed to epididymo-orchitis, haematuria to infection and chronic retention with overflow, perhaps combined with severe obstructive uropathy, to the incontinence of senility.

The responsibility of the hospital specialist in establishing a diagnosis and commencing treatment promptly begins with receipt of the family doctor's referral letter. Delay in this process will discourage prompt referral. Delay in the out-patient clinic can be reduced by increasing (within the limits of finance and manpower) the number of patients seen. This process is facilitated by minimising administrative inadequacy. Results of investigations are commonly unavailable and patients' notes become misplaced (Duncan *et al.*, 1988). These problems should be largely solved by the establishment of on-line computerisation of records.

Urologists have paid close attention to the optimal use of day care facilities and local anaesthetic techniques. They have been particularly energetic in exploring the use of modern sedative drugs and their specific antagonists. Without question these innovations will revolutionise the management of common problems and lessen the load on restricted in-patient resources. Standard-

ised regimes for investigation in symptom clinics (e.g. haematuria, infertility, impotence) can reduce waiting times. Bottlenecks further down the line of management must also influence waiting time. For example, there has been much criticism of the inefficiencies of traditional practices in the use of operating facilities (Dudley, 1988). Changes to maximise their use will be mandatory for hospitals attempting to pay their way. Such changes will require additional expenditure initially and considerable upheaval in reorganisation. It is uncertain whether this is justified in terms of reduced morbidity and perhaps mortality.

Delay in the management of specific diseases—does it matter?

Malignant disease. A patient ultimately diagnosed as having an incurable cancer may in retrospect bitterly resent any delay in his management. He will have in mind the generally accepted notion that (a) there is a natural transition from pre-malignancy through superficial non-invasive localised disease to bulky invasive primary disease with metastases, (b) earlier diagnosis identifies smaller tumours at an earlier stage when radical treatment is feasible, and (c) survival is improved by screening for pre-symptomatic disease and by establishment of symptom clinics where there is open access to diagnostic facilities.

The alternative view is that progression of cancer is established at an early stage in its life history as a molecular event which cannot be recognised or anticipated. It is therefore pre-determined and inevitable (McDonald, 1951). Furthermore, analysis of survival in relation to treatment and its timing may fail to take account of statistical artefact (Mettlin and Natarajan, 1987). Two examples are (a) lead time bias—earlier diagnosis may appear to extend survival in patients who ultimately die but the effect may be nothing more than advancing time of recognition along the biologically pre-determined life history of the tumour (Feinleib and Zelen, 1969), and (b) the effects of modern diagnostic techniques—comparison of a modern series with historical controls can be biased by diagnosing lesions as early cancer in the later series which would have been disregarded in the earlier series. Similarly, historical metastatic disease may have a worse prognosis than contemporary metastatic disease diagnosed at an earlier stage (Feinstein *et al.*, 1985).

These controversial issues will be discussed for 2 common urological malignancies.

Bladder cancer. The malignant potential of every bladder tumour must not be underestimated. However, less than 5% of well-differentiated tumours which have not breached the basement membrane progress locally and fewer metastasise. These form 70 to 80% of all bladder tumours (Heney *et al.*, 1982). Much effort is expended by urologists in attempting to reduce delay in the initial diagnosis and in cystoscopic follow-up of superficial tumours, in the hope that progression to a higher grade or stage can be anticipated; and yet invasive tumours may never originate in superficial growths.

In a study on patients with invasive cancer, a history of papillary tumours was obtained in only 20%; in a further 20% a cystoscopy had by chance been performed in the recent past and showed no evidence of papillary neoplasm (Brawn, 1982). Other studies on step sections of cystectomy specimens of invasive tumour rarely showed papillary elements (Kakizoe *et al.*, 1984). It may be inferred that invasive bladder cancer does not usually originate in recognisable superficial papillary tumours and there is little to be achieved in terms of survival by reducing diagnostic delay. Nevertheless, early diagnosis may in some circumstances be beneficial for the small proportion of patients with superficial tumours likely to become invasive or with invasive tumours which have not yet metastasised.

The consensus from a number of retrospective analyses was that crude survival could be increased by 10 to 20% if the diagnosis was made within 1 month of the onset of symptoms (Wallace, 1985). These data may have given impetus to the establishment of symptom clinics. Hendry *et al.* (1981) described the benefits of such a haematuria service where patients could undergo IVU and cystoscopy within a week of referral. They compared staging of bladder tumours thus diagnosed in a 2-year period with that of patients whose tumours were diagnosed conventionally in the preceding 4 years. The results were disappointing in that they showed a minimal shift (6%) in the proportion of T3 to T2 tumours and an insignificant difference between T4a and T4b tumours. These distinctions are obviously very subjective when based on clinical assessment.

Screening of populations at risk of developing bladder cancer should improve the survival rate by identifying tumours before they become invasive, with a corresponding improvement in prognosis. In fact, retrospective assessment of workers in high risk industries who were subject to regular urine cytology showed only marginal differences in

survival over other groups of patients presenting routinely to a urology clinic (Cartwright *et al.*, 1981). The authors acknowledge the problem of lead time bias and of inaccurate death certification in their analyses.

The treatment of deeply invasive bladder cancer and virtually all solid tumours is unsatisfactory in that 60 to 70% of patients die with metastatic disease within 5 years. The hope is that few patients would reach the stage of invasion if better diagnostic techniques could be applied with less delay or if features indicative of a poor prognosis could be identified in the original superficial tumour. At present both prospects seem hopeless (Abel, 1988).

More timely investigation of potential symptoms of bladder cancer seems desirable to allay the patient's anxiety, although it will probably do little to alter the prognosis. Until better forms of treatment are developed, the degree of reorganisation involved in establishing haematuria clinics seems unjustified.

Testis. There may be greater justification for minimising the delay in diagnosis of germ cell tumours of the testis. Larger primary tumours tend to be associated with the development of metastases. In Denmark, where public awareness of testicular self-examination is perhaps most encouraged, the size of tumour at presentation appears to be falling, and with that a reduced risk of nodal disease (Jacobsen *et al.*, 1984).

A comprehensive study of the Irish Testicular Tumour Registry (Thornhill *et al.*, 1987) showed a clear difference between Stage I and Stage II disease. On the other hand, the delay in Stage III and Stage IV disease was less than for Stage II, presumably because more advanced disease had a more dramatic and therefore an earlier presentation. Fossa *et al.* (1981) were in the minority in finding no effect of delay on stage distribution.

As for other solid tumours, it is difficult to find firm evidence that in any one patient a small tumour restricted to the testis will progress in a given time to subdiaphragmatic lymphatic spread and thence to supradiaphragmatic lymphatic and haematogenous spread. It is clear that the pattern of progression can be very variable and there may even be complete disparity between the behaviour of the primary tumour and progression of metastases. It is perhaps only with rapidly growing trophoblastic tumours that a clear pattern of progression from primary to metastatic disease can be clearly seen and then only because such tumours tend to behave more aggressively and progress within the short

periods of delay between suspected diagnosis, orchiectomy and staging procedures.

The treatment of carcinoma of the testis has been revolutionised by the introduction of effective chemotherapy regimes (Peckham, 1985). Diagnostic delay now seems less important. Metastatic disease in abdominal lymph nodes and even small lung metastases will usually respond to treatment with a normal life expectation. However, there is still room for improvement and bulky metastatic disease and widespread haematogenous disease beyond the lung has a worse prognosis (Peckham *et al.*, 1988). It is also generally agreed that delay may be critical in the response of more advanced disease to chemotherapy. In the study by Oliver (1985), patients dying with drug-resistant metastatic disease had an average delay of 7 months between presentation and diagnosis, whereas those whose metastases were cured by chemotherapy had a mean delay of 4 months. In the study by the MRC Working Party on Testicular Tumours (1985), the 3-year survival rate when the delay was less than 3 months was 81% and 61% when it was more than 3 months. A selected series of patients treated in Minneapolis by Bosl *et al.* (1981) also demonstrated a diminishing likelihood of increasingly bulky disease to respond to chemotherapy even when complemented by retroperitoneal nodal clearance in high stage disease.

Summary. It is unlikely that a patient with a suspected testicular tumour will remain long on a urological waiting list and most of the delay before diagnosis is due to the patient being unaware of the potential gravity of a testicular swelling. The General Practitioner may contribute by treating him for epididymo-orchitis on the mistaken assumption that pain and inflammation exclude a tumour. It is certainly possible for the urologist to make an incorrect diagnosis but nowadays, even when this is virtually certain, there is a tendency for it to be confirmed by scrotal ultrasonography.

Whilst survival will probably not be much affected, widespread screening, particularly of vulnerable groups (cryptorchidism, infertility) will provide larger numbers with low volume localised disease and therefore less requirement for potentially dangerous chemotherapy.

Benign Disease

Two examples are chosen for discussion of the potential hazards of delayed management.

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Bladder outflow obstruction—prostatic disease. The commonest reason for male out-patient referral in an adult western-style urological practice is prostatism. An assessment of the length of a urologist's waiting list is often seen in terms of the number of patients requiring transurethral resection of the prostate and the time between diagnosis and routine admission. It is not exceptional in the United Kingdom for a non-urgent patient not to be admitted to an NHS bed until he develops retention. However, it is likely that in many cases waiting lists are overburdened by patients for whom prostatic surgery would be unnecessary. "Prostatism" is apt to be poorly understood even by urologists (Turner-Warwick, 1979). Typical prostatic symptoms may not necessarily indicate obstruction. When it is present it may not be progressive. In a study from Bristol, Ball *et al.* (1981) showed that only 67% of 380 patients referred with symptoms were urodynamically obstructed; 107 patients did not undergo surgery and were followed up for a minimum of 5 years. Only 25% had deteriorated, 10 having undergone transurethral resection. From these and other data there seems little doubt that the simple assessment of urinary flow rate and of residual urine by ultrasound of all patients presenting with prostatism would probably allow most urological waiting lists to be decimated.

Selective α -blocking agents can help to relieve symptoms of prostatism during the period of delay. Judging from the increasing number of drugs which are becoming available, the pharmaceutical industry expects to capitalise on long waiting lists for TURP.

There are several potential risks in delaying planned prostatic surgery.

Obstructive nephropathy. The patient may have chronic retention and is therefore at risk of developing secondary obstructive nephropathy (George *et al.*, 1983). The presenting symptoms of this particular syndrome are usually mild and progression to severe and perhaps irreversible renal impairment may be insidious. The painless, non-tender enlargement of the bladder may easily be missed and even mis-diagnosed.

Most patients at risk may be identified for timely treatment by routine estimation of blood urea, electrolytes and creatinine and assessment of residual urine and upper tract dilatation by urography or ultrasound. Logically, this minimum assessment should be repeated at intervals since rapid progression from normal calibre to dilated ureters

can occur, even if simple initial investigations were satisfactory. Urodynamic assessment of patients presenting with outflow obstruction might separate low pressure from high pressure chronic retention and both from simple outflow obstruction, but availability of this facility may be limited due to lack of resources.

Prostate cancer. Clinically undetectable prostatic cancer may progress. The prevailing attitude to the treatment of early prostate cancer in the UK tends to be nihilistic. The tumour is generally regarded as slow-growing and few lives are likely to be saved through pre-empting the transition to metastatic growth by attempting a cure for all by radical prostatectomy or radiotherapy.

In fact, up to 20% of T0 tumours (A1) will progress locally to produce significant mortality by 10 years (Epstein *et al.*, 1986). There is no doubt that in most of the remainder of the developed world the risk of occult cancer progressing during a long sojourn on a urological waiting list would be regarded as significant and unacceptable.

Transrectal ultrasound with guided biopsy of suspicious echogenic foci and serum PSA performed on all patients with prostatic obstruction would certainly facilitate the diagnosis of occult cancer (Allhoff *et al.*, 1988). In particular, PSA corrected for prostatic volume measured directly by transrectal ultrasound may provide a better screening test for malignancy. However, the question of the benefits of early diagnosis and treatment of low-stage localised prostate cancer is likely to remain unresolved for years to come.

Bladder cancer. "Prostatism" may be due to bladder cancer rather than benign prostatic hyperplasia. This differential diagnosis is more likely if there are irritative symptoms, *i.e.* frequency, urgency and nocturia due to secondary instability and predominating over the mechanical effects of obstruction. Haematuria, historically or on urine microscopy, should advance a patient up the waiting list with the possibility of bladder cancer in mind.

The risk of acute retention. It is remarkable how few patients with prostatism decompensate to develop acute retention whilst on a long waiting list for transurethral resection. In one report this occurred in only 2% (Ball *et al.*, 1981). However, any patient with bladder neck obstruction remaining on a long waiting list will be susceptible to the retention-provoking effects of diuretics, broncho-dilators,

alcohol and a high fluid intake, prolonged recumbency and cerebrovascular disease.

Patients presenting for TURP with an indwelling catheter are more susceptible to infective complications. However, in circumstances where it was impossible to deal with every patient immediately, Higgins *et al.* (1981) showed that there was no significant disadvantage in maintaining a "catheter waiting list".

Cryptorchidism. Children with testicular maldescent often reside on long waiting lists, although most surgeons try to ensure that orchiopexy is performed at the latest before school age. This is because spontaneous descent of the testes later on in childhood is no longer recognised and if benefit is to be maximised in terms of risk of malignancy and germ cell function, the operation should be performed as soon as possible after diagnosis. However, it is doubtful whether early surgery reduces the tendency for these complications to develop (Martin, 1982).

It has not been shown conclusively that sperm morphology is better preserved in patients undergoing early rather than late orchiopexy (Hezmall and Lipshultz, 1982), though of course it is necessary to study the much smaller number of patients with bilateral maldescent. Abnormal function could still be a primary congenital abnormality rather than an acquired effect (Hinman, 1989).

All discussions of the risks of an undescended testis and the benefits of early treatment depend on an accurate assessment of the prevalence of maldescent in the population. It could be frequently misdiagnosed. In any event, there has been an apparent doubling of the frequency of cryptorchidism during the past 20 to 30 years (Lancet, 1989). In a carefully controlled study, the cryptorchidism rate at the age of 3 months was 6 to 7 times greater than a much quoted figure from 40 years ago (John Radcliffe Cryptorchidism Study Group, 1988). This rise would obviously reduce the computed relative risk of testicular tumour.

In another closely observed group of patients from Copenhagen, there was no increase at all in the risk of development of testicular tumours amongst cryptorchids (Giwerzman *et al.*, 1981). The majority of patients in this controversial study had undergone orchiopexy, though at a comparatively late mean age (10.3 years) compared with present standards. Nevertheless, orchiopexy could have given some protection to this group from developing testicular tumours. However, the slightly increased risk of tumour development in

the contralateral descended testis, and of subfertility in unilateral cryptorchidism, suggests that nature predominates over nurture and hence delay in treatment causes little disadvantage.

Summary

Statistics on urological waiting lists suggest that there is considerable regional variation in delay before treatment. This clearly depends on many factors but is unlikely to indicate significant variation in morbidity either at presentation or during subsequent admission for surgery.

Managers and politicians should be extremely wary if encouraged to base major changes in distribution of funding and equipment on a casual examination of waiting list figures. It is doubtful if delay in diagnosis or treatment seriously influences morbidity and mortality from urological illness.

Acknowledgement

I am grateful to Sue Day who patiently prepared the typescript.

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Identification of Urinary Stone Composition by Pulsed Dye Laser

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Summary—Stones were recovered from the urinary tract and their composition determined by X-ray diffraction before exposure to a pulsed dye laser beam. The resultant fluorescent emissions were recorded using a scanning reticon and they appeared to be specifically related to the composition of each stone.

This technique has a practical application as it may allow identification of the composition of urinary tract stones *in vivo*, and so indicate the best mode of lithotripsy.

The management of urinary tract stones involves not only removal of the stone but also treatment to prevent its recurrence. In both cases it is important to ascertain the composition of the stone. It is also advantageous if the composition can be determined rapidly in order to commence treatment or change to a more suitable form of treatment. We describe a method using a pulsed dye laser which allows stone composition to be analysed rapidly.

Materials and Methods

Urinary stones or stone fragments that had been removed by open or percutaneous surgery were analysed by X-ray diffraction to determine their composition (Sutor, 1982). The same stones were then subjected to laser analysis by the following method.

A Vuman PDL-10 pulsed dye laser was set up to deliver 100 mJ pulses of light of 1 μ s duration at 504 nm through a 300 μ optical laser fibre. An identical fibre (the analysis fibre) was positioned adjacent to the first but with the tip stepped back about 2 mm; the other end of this fibre was inserted into the entry port of a 512 element solid state scanning photo-diode array. The output from the diode array was connected to a digital storage

oscilloscope (Philips PM 3315 (U)) which was in turn connected to an X–Y plotter. The storage oscilloscope was triggered by the laser pulse, synchronised to the scanning of the diode array. This arrangement permitted urinary stones to be exposed to pulses of laser light, with any resulting fluorescence collected, analysed and stored as hard copy.

Each stone was placed in a small laboratory beaker and covered with normal saline or freshly voided urine. The laser fibre and the analysis fibre were held in a retort clamp in such a position that the laser fibre was approximately 1 mm above and perpendicular to the stone surface. The laser was then fired and any resulting optical spectra recorded first on the storage oscilloscope and then on the X–Y plotter. Figure 1 shows the equipment diagrammatically. Each stone was analysed repeatedly in both saline and urine and 4 or 5 stones from each composition group were examined.

Results

In most instances only 1 laser pulse was required to produce a good record of fluorescent emission. The spectra obtained are shown in Figures 2 to 7, where the differences recorded from stones of various compositions are easily seen. Each spectrum was found to be specific for stones of identical compo-

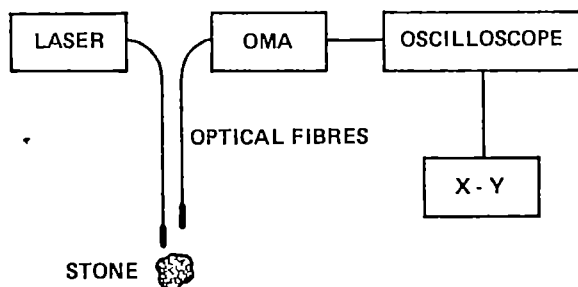


Fig. 1 Diagrammatic representation of equipment. OMA=optical multichannel analyser. X-Y=X-Y plotter.

sition and was constant for varying positions on each stone. In this respect, the overall shape and configuration of the spectra are characteristic for each stone composition. Identical results were obtained when stones were analysed in saline or urine.

Spectra were easily obtained from calcium oxalate, carbonate-apatite, struvite and hydroxy-apatite stones; in most cases several peaks on the spectrum could be identified, indicating the presence of calcium in the stone (see arrows on Figs 2, 3 and 5). All of the recorded spectra contained a peak at 500 nm due to the recording of the incident laser light (marked L on each spectrum). It was found that the spectra from calcium oxalate monohydrate and dihydrate differed in the 550–650 nm wavelengths.

We found it difficult to obtain spectra readily from stones composed of cystine, uric acid and brushite. These stones often needed several pulses before emission could be detected, the emission occurring only when a "crack" was heard, signifying, possibly, that a plasma field had been produced in response to the laser pulse. If no such noise was audible the only recording obtained was reflected

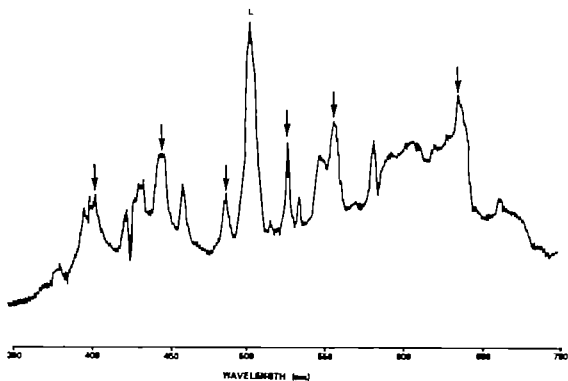


Fig. 2 Spectrum from a calcium oxalate monohydrate stone. L=laser wavelength.

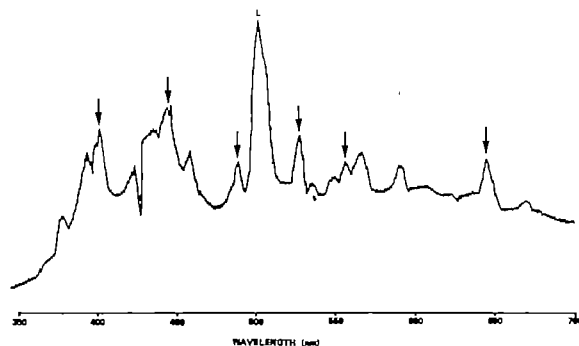


Fig. 3 Spectrum from a calcium oxalate dihydrate stone. L=laser wavelength.

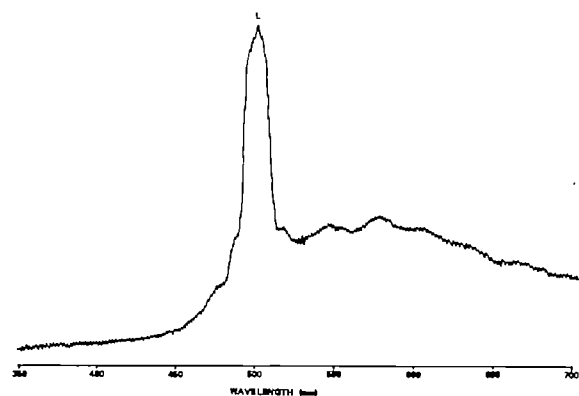


Fig. 4 Spectrum from a pure uric acid stone. L=laser wavelength.

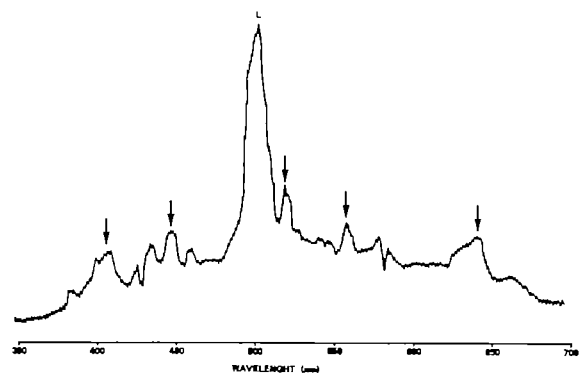


Fig. 5 Spectrum from a struvite stone. L=laser wavelength.

laser light (Fig. 8). It was also noted that all of these stones had a smooth surface and they fragmented less readily in response to the laser.

Discussion

Until recently, urinary tract stones were removed by open surgery or, in a few selected cases, by

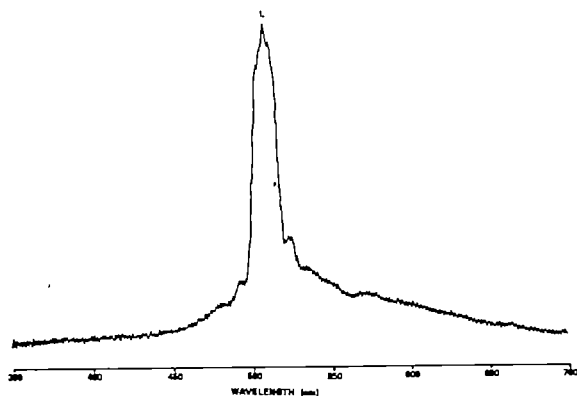


Fig. 6 Spectrum from a cystine stone. L=laser wavelength.

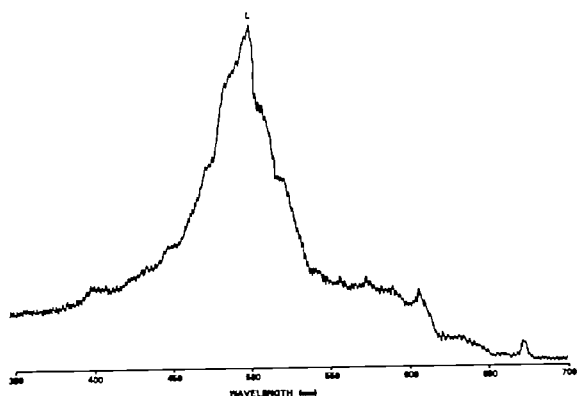


Fig. 7 Spectrum from a brushite stone. L=laser wavelength.

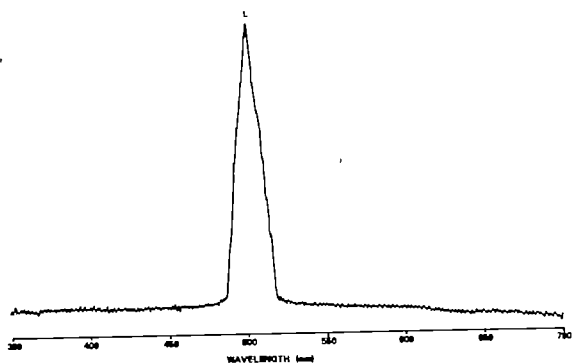


Fig. 8 Spectrum showing reflection of laser light from surface of a stone. L=laser wavelength.

simple basket extraction. The advent of percutaneous surgery and ureteroscopy with ultrasound, electrohydraulic and more recently laser disintegration (Tanahashi *et al.*, 1981) has reduced the need

for open surgery. The use of lasers for the removal of urinary tract stones is not new, since Mulvaney and Beck (1968) tested the effect of continuous wave CO₂ lasers on calculi *in vitro*; they were found to be unsatisfactory because they caused thermal damage to urothelium. More recently, the transmission problems of Q-switched Nd-YAG lasers along optical fibres were found to prevent their effective use in stone fragmentation (Watson *et al.*, 1983). The safe destruction of stones with a laser has become practical only in the last few years with the development of the pulsed dye laser (Watson and Wickham, 1986). The arrival of extracorporeal shockwave lithotripsy (ESWL) has further revolutionised the management of stones. Nevertheless, stones are still encountered which are resistant to disintegration by some or all of these modern techniques.

Ready (1971) suggested that when pulsed laser energy is applied to a target, the energy is absorbed, causing initial vaporisation and subsequent absorption of more laser energy into this vaporised material, leading to plasma formation. Teng *et al.* (1987) concluded that the formation of the plasma was necessary for stone fragmentation, because as the plasma itself absorbs more laser light it expanded and created an acoustic transient which caused damage to the stone. The activity within the plasma, involving complex interactions between electrons, ions and atoms, also resulted in the emission of detectable spectra. The atoms and ions involved in this plasma formation derive from the stone itself and the recorded spectra should therefore be specific for any individual composition of stone.

Stones commonly encountered in urological practice are calcium oxalate monohydrate, calcium oxalate dihydrate, struvite and, to a lesser extent, stones composed of uric acid, cystine and calcium phosphate.

The technique we describe distinguishes between most of these compositions. Calcium oxalate monohydrate and calcium oxalate dihydrate can be distinguished by the differences in their respective spectra in the 550–650 nm wavelengths (Figs 2 and 3). Similarly, the shape of the spectra from 520–700 nm obtained from a struvite stone allows this to be differentiated from both calcium oxalate monohydrate and calcium oxalate dihydrate (Figs. 2, 3 and 5), the spectra from struvite being flatter with less well pronounced spikes. In contrast, the spectra from uric acid stones reveal a wide flat continuum from 525 to 700 nm, again a finding specific to this stone composition.

We agree with Meyer *et al.* (1988) that if a stone contains calcium, peaks will be found on the spectrum to indicate its presence, as indicated by arrows in Figures 2, 3 and 5.

We found it difficult to obtain spectra from cystine and brushite stones but believe they were emitted when an acoustic "crack" was heard as the laser was fired on to the stones. If no "crack" was audible, the recording consisted purely of a laser light reflection from the stone surface (Fig. 8). This is clearly different from recordings obtained from the cystine and brushite stones shown in Figures 6 and 7. The spectrum obtained from uric acid stones (Fig. 4) also differs from the recording of pure reflection and again confirms that a plasma had been formed.

Unfortunately, we have not been able to obtain sufficient quantities of brushite calculi (calcium hydrogen phosphate dihydrate) to establish whether it is possible to distinguish the composition of this stone from that of other calcium phosphate calculi. Stones of mixed composition may also present problems. The composition of the surface can be analysed but the core is not accessible until the stone has fragmented.

The use of a pulsed dye laser with a scanning diode array is an effective method of stone analysis. The main advantages of this technique are speed, low cost of additional equipment to a unit already possessing a laser and the ability simultaneously to analyse and/or disintegrate a stone *in vivo*. Certain types of stone, such as brushite, do not respond well to laser lithotripsy (Dretler *et al.*, 1987). If such a stone is encountered during an operation, this technique would allow rapid identification of its composition and suggest an alternative fragmentation device that might result in more rapid disintegration.

Speed of analysis is not the only point in favour of this method of stone identification. The time honoured method of quantitative chemical analysis, although inexpensive in terms of materials, is time-consuming and hence costly. X-ray diffraction analysis, although very sensitive, is not a readily available technique. Despite the accurate results obtained by these methods they are applicable only *in vitro*. The only other method that enables urinary stones to be analysed *in vivo* is computed tomography (CT). This relies on the principle that stones of different composition have different radiation absorption. Although it seems a simple, non-invasive procedure, CT scanners vary and each unit must establish its own absorption parameters for each type of stone (Mitcheson *et al.*, 1983). The use

of CT scanning also exposes the patient to radiation.

These results suggest that it is not just the hardness of the stone that influences fragmentation but also the stone surface characteristics. Stones with a dark surface fragment well due to good absorption of laser energy, whereas those with a pale, reflective surface absorb little energy and fragment poorly, if at all. A similar phenomenon was observed by Teng *et al.* (1987) when studying the effect of a pulsed dye laser on biliary stones. We feel it might be possible to coat the surface of a stone with a dye prior to laser lithotripsy, thereby increasing the absorption of the laser light. We have attempted to do this but a suitable dye has not yet been found that is applicable to the *in vivo* situation, although methylene blue is a possibility.

The method we have described could be further refined to yield more accurate results. The fluorescence emitted from the stone surface in response to the laser pulse could be analysed on a much larger spectrometer and the Raman shift phenomena explored (Daudon *et al.*, 1983). This technique is widely used in industry and geology, but its application to the *in vivo* clinical situation is probably impractical as the spectrometer needed to detect the small amounts of infra-red light is extremely large. In contrast, our equipment occupies a small desk top.

Meyer *et al.* (1988) and Helfmann *et al.* (1988), in similar studies used more complex equipment to analyse the emission spectra from urinary calculi. The recordings were found to be composed of a continuum upon which were superimposed absorption and emission lines from the constituent atoms and ions. They found that the recorded spectra varied with time following the laser flash. Our equipment did not permit the investigation of this time effect but all emissions from the stones over a time exceeding 1000 μ s were recorded as a single cumulative spectrum.

With more sophisticated equipment incorporating beam splitters becoming available, it should be possible to use a single optical fibre to deliver the laser pulse and to relay the emission from the plasma for analysis. Although this system works successfully when mounted on a vibration-free optical table in the laboratory, any movement in the clinical situation would result in a rapid loss of optical alignment and consequent loss of spectra recording.

Despite the fact that absolute accuracy of stone analysis is not always possible, we have successfully recorded emission spectra from stones of urinary

tract origin and these spectra allow the composition of the stone to be determined with a fair degree of accuracy in most cases.

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Long-term Follow-up of Children with Renal Carcinoma

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Summary—Renal carcinoma is a rare tumour in children. The clinical, histological and follow-up details of 6 patients are presented. Haematuria is confirmed as an important indicator of renal pathology. Long-term follow-up suggests that chemotherapy and radiotherapy have little effect on the prognosis in advanced disease.

Renal carcinoma is an unusual tumour in the paediatric population, accounting for less than 3% of all childhood renal malignancies (Lack *et al.*, 1985). Because of its rarity, few reports exist with more than single case histories (Raney *et al.*, 1983). The aim of this study was to assess our own experience and examine the role of radiotherapy and chemotherapy in the management of this neoplastic condition.

Patients and Methods

A review of the records at the Manchester Children's Tumour Registry disclosed relevant data on 6 patients with renal carcinoma in the period from 1968 to 1987. The case records were surveyed and information concerning the clinical findings, surgery, histopathology, adjuvant therapy and outcome was assimilated. In spite of thorough pre-operative investigation and per-operative assessment, diagnosis could only be made on histopathological grounds following review by a tumour board of renowned pathologists.

Results

Clinical features

The patient's average age was 9 years at the time of diagnosis (range 3.5–14 years). All were male.

The commonest presenting symptoms were ab-

dominal pain, affecting 4 boys, and haematuria in 5 (Table). In 1 patient (in whom there was no haematuria) the pain was severe enough to mimic acute appendicitis for which surgery was performed. In 2 others, acute ureteric colic was diagnosed. The duration of symptoms depended on their severity; 2 children had had intermittent painless haematuria for 4 to 5 months before referral for further investigation.

On examination, 5 patients had a palpable abdominal mass. One boy was found to have a left-sided varicocele and was also noted to be hypertensive (140/100). All 6 patients were clinically anaemic but only 5 had abnormal haemoglobin levels at presentation.

Investigations

Radiological investigations included plain abdominal and chest X-rays, intravenous urography (IVU), inferior vena caval venography, ultrason-

Table Details of 6 Male Patients

Case No.	Age (years)	Pain	Haematuria	Stage	Outcome
1	11	+	—	I	Alive
2	14	+	+	I	Alive
3	12	—	+	III	Dead
4	3.5	+	+	II	Alive
5	9	—	+	I	Alive
6	14	+	+	IV	Dead

Accepted for publication 27 September 1989

ography and computed tomography. Isotope bone and liver scans were also carried out. In 2 patients abnormal calcification was detected on plain abdominal X-rays. In all cases the IVU was abnormal, demonstrating filling defects, with distortion of the renal calyces. When performed, ultrasound and CT examinations confirmed the suspicion of intrarenal pathology. However, in no patient was the diagnosis of renal carcinoma made pre-operatively. In 1 patient there was a suggestion of hilar lymphadenopathy on chest X-ray and this boy eventually went on to develop a pleural effusion and died from metastatic disease.

Pathology

There were 4 tumours of the right kidney and 2 of the left. In all resected specimens the macroscopic growth was large, ranging in size from 5 to 15 cm. The tumours all had a bulging, variegated appearance with areas of firm neoplastic tissue, haemorrhage, necrosis and cystic involution.

On histological examination the pathology was easily identifiable as renal adenocarcinoma in 5 cases. In 1 patient transitional cell epithelium was predominant but the final diagnosis was confirmed as renal carcinoma by our tumour board. Three tumours had clear cell morphology and 2 were tubulopapillary in character.

Vascular invasion was confirmed in 1 patient with tumour noted to extend from the renal vein into the inferior vena cava.

In 3 patients the tumour was assessed as stage I disease with the tumour confined to the kidney. The tumour was noted to have breached the renal capsule in 1 case, making it stage 2 disease. In 1 patient regional lymphatic nodal involvement made the grading stage III and in the other patient metastatic spread was assumed, based on chest X-ray findings.

Treatment and Follow-up

Surgery

The patient who presented with signs of peritonitis underwent appendicectomy and a partial nephrectomy at another hospital and was referred for further treatment once the diagnosis was established. Total nephrectomy was then performed. The other 5 boys underwent total nephrectomy via an abdominal approach with sampling of the para-aortic nodes. A second laparotomy was undertaken to assess the extent of local recurrence in 1

unfortunate child and this patient also had an exploratory thoracotomy before he died.

Adjuvant treatment

In 1 patient radical nephrectomy was assumed to be curative and no further therapy was deemed necessary. In another, with stage 2 disease, a course of radiotherapy was given, with the patient receiving 3000 cGy to the abdomen over a 36-day period. The 2 patients with advanced pathology underwent combination chemotherapy with radiotherapy. Vincristine, doxorubicin, actinomycin D and cyclophosphamide were administered with 2060 cGy abdominal radiotherapy to 1 patient who, in addition, received vinblastine and bleomycin before he eventually died. The other patient who died also received intensive adjuvant therapy with sequential vincristine, actinomycin D and norethisterone, which were the recommended agents at the time. This boy received 3000 cGy to his abdomen and mediastinum, and 2 courses of radiotherapy consisting of 1250 and 3000 cGy to his spine with little response. The 2 remaining patients underwent radiotherapy (3000 cGy each to the abdomen) and chemotherapy, consisting of actinomycin D in 1 case and vincristine in the other.

Follow-up and survival

The surviving patients were reviewed on a regular basis over a period ranging from 2 to 20 years. The 2 children who died lived for 6 and 18 months after diagnosis and radical nephrectomy. Two of the surviving patients had seminal abnormalities: 1 had low seminal volume and the other infertile sperm counts.

Discussion

Renal carcinoma is so unusual in the young that it has been difficult to define the natural history of the disease. As illustrated by our patients, a tendency to regard and treat the children as having Wilms' tumour has evolved (Raney *et al.*, 1985). Unfortunately, this has not resulted in the same success that has been achieved in Wilms' tumour (Gough, 1989).

The aetiology of renal carcinoma in children is not known. It has been suggested that the development of malignancy is a complication in the multicystic dysplastic kidney (Shirai *et al.*, 1986), but only 1 such case has been reported in children (Birken *et al.*, 1985). None of our patients had multicystic dysplasia on histological examination.

The significance of frank haematuria in a child cannot be overstated, especially when there are no other symptoms or history of trauma (Hartman *et al.*, 1982). Two of our patients had painless haematuria for several months before investigations could be arranged and 1 of these children eventually died. The classical triad of loin pain, haematuria and an abdominal mass seen in adults was also a common feature in our patients (Hicks *et al.*, 1975; Chan *et al.*, 1983).

The management of renal carcinoma is surgical (Raney *et al.*, 1983). Radical nephrectomy will cure stage 1 disease and almost certainly stage 2 (Herschorn *et al.*, 1979). Excision of regional lymph nodes has been advocated to improve the accuracy of staging and to plan adjuvant therapy (Lack *et al.*, 1985). In addition, removal of the most likely source of metastatic disease may enhance the chances of cure. Because of the low incidence of renal carcinoma and the small number of patients, it is difficult to assess the efficacy of adjuvant therapeutic regimes in a controlled fashion (Abrams *et al.*, 1979). The role of chemotherapy and radiotherapy cannot therefore be clearly defined (Castellanos *et al.*, 1974).

Despite intensive research and clinical efforts, metastatic disease in adults remains resistant to therapy and this also appears to be the case with children (Lack *et al.*, 1985). In the past, the criteria for adjuvant treatment have been based on treatment protocols for Wilms' tumour, with little evidence of success. Chemotherapeutic regimes have significant side effects and infertility problems were recorded in 2 of our 3 patients who survived after receiving chemotherapy. Since there is little evidence that adjuvant treatment has a role, there is a need for appropriate controlled trials to examine this.

Chemotherapy and radiotherapy may well help to relieve the symptoms caused by metastatic

disease but our review suggests that they have little effect on the eventual prognosis. In view of the severe side effects induced by these modalities, especially in children with advanced pathology, the use of adjuvant therapy in this condition demands serious consideration.

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Staghorn Calculi of the Kidney: Classification and Therapy

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Summary—Following the introduction of new techniques, the reclassification of staghorn calculi is indicated in order to establish the most suitable form of treatment.

Of 269 patients with staghorn calculi treated over a 3-year period, 56% underwent extracorporeal shockwave lithotripsy (ESWL) monotherapy; 16% required open surgery and the remaining 28% underwent percutaneous nephrolithotripsy (PCNL) with ultrasound in association with ESWL. The latter group has been reviewed, taking into account invasiveness, results, complications and cost effectiveness. A combination of PCNL and ESWL was beneficial in patients in whom percutaneous access through a single tract removed more than 70% of the stone. As a result of these findings, the authors propose a revised classification of staghorn calculi.

The definition of renal staghorn calculi is far from clear-cut. It should indicate a large stone filling all of the calices and renal pelvis. However, with the introduction of new therapeutic procedures for the treatment of urinary tract stones (Chaussy *et al.*, 1980; Wickham and Kellet, 1981; Alken *et al.*, 1981; Perez-Castro Ellendt and Martinez Pineiro, 1982; Whitfield, 1983), these concepts need to be revised according to quantitative criteria.

The treatment of staghorn calculi with caliceal branches is controversial because of the wide range of therapeutic approaches available, either extracorporeal, percutaneous or surgical, alone or in association (Wickham, 1979; Clayman *et al.*, 1983; Brannen *et al.*, 1985; Eisenberger *et al.*, 1985; Snyder and Smith, 1986; Di Silverio *et al.*, 1987; Segura, 1989).

We have reviewed our experience in order to draw up some guidelines and to classify staghorn calculi according to the most suitable form of treatment.

Patients and Methods

Between January 1985 and July 1988 we have treated 269 patients with staghorn calculi. The male

to female ratio was 1.6 and the age range was 7 to 78 years (average 38.5). Calculi were recurrent in 34.6% of cases. For ESWL we used a Dornier HM3 lithotripter; for PCNL a Storz nephroscope with ultrasound generator was used. Either an indwelling ureteric catheter or a double-J stent was placed prior to undertaking ESWL monotherapy. 56% of patients underwent ESWL monotherapy in average 1.6 sessions; 28% of patients underwent a combination of PCNL and ESWL. PCNL was performed through a single renal tract via the lower calix. Subsequently, starting 5 days after PCNL, 1 to 4 ESWL sessions were performed (average 1.8); 16% of patients underwent open surgery with lower pyelocalicolithotomy and multiple anastrophic nephrotomies under echo or Doppler guidance.

Plain abdominal film, intravenous urography, renal ultrasound and complete blood examination as well as urine analysis were carried out in all patients prior to treatment.

We considered as stone-free those patients who were without residual fragments as assessed by radiological and ultrasonographic checks 3 months after treatment.

Complications included subcapsular haematomas after ESWL, prolonged bleeding after PCNL which required blood transfusion, septic fever and urinary tract obstruction which all required addi-

tional treatment. The cost/benefit ratio was evaluated according to the mean cost of hospitalisation (in Italy 192 US\$/day). Operative expenses accounted for a 5% increase in the total hospital stay for ESWL monotherapy, a 10% increase for PCNL+ESWL and a 20% increase for open surgery. Patients undergoing ESWL had an extra charge of 380 US\$ for each electrode.

Results

Seventy-eight per cent of the patients having ESWL monotherapy, 81% of those treated with PCNL+ESWL and 83% of the patients operated upon are completely stone-free. One patient (0.66%) who had undergone monotherapy ESWL developed a subcapsular haematoma and needed blood transfusion. Blood transfusion was also required in 5.2% of patients treated with PCNL+ESWL and in 35% of those having open surgery.

Septic fever occurred in 45% of patients having ESWL monotherapy, in 55% of those treated with PCNL+ESWL and in 29% of those undergoing open surgery.

Symptomatic obstructive complications of the urinary tract occurred in 15% of patients undergoing ESWL monotherapy and in 25% of those treated by PCNL+ESWL; patients who were operated upon did not have this complication. In all cases, obstruction was successfully treated by operative ureterorenoscopy (URS).

The mean cost of treatment was 3957 US\$ for ESWL monotherapy (mean hospital stay 12 days) and 5565 US\$ for combined PCNL and ESWL (mean hospital stay 20 days); surgery had a mean cost of 3230 US\$ (mean hospital stay 14 days).

Discussion

These results demand an analysis of the criteria leading to the various forms of treatment. Small stones which entirely fill a small pyelocaliceal system should be regarded as staghorn calculi; 150 patients with such stones successfully underwent ESWL monotherapy in 1 or 2 sessions and we regard this as the treatment of choice.

Open surgery was first-line treatment in 43 patients with giant staghorn calculi (>10 cm in diameter and 5 cm in thickness) with equal distribution throughout the pyelocaliceal system.

There is, however, a wide range of staghorn calculi between these two extremes and they require a combination of PCNL and ESWL. With regard to PCNL, we recommend access through a single

rather than multiple tracts, since the latter procedure increases the risk of bleeding and parenchymal damage.

Differences in stone size and stone burden mean that these calculi cannot be easily compared. Thus we have reviewed the 76 patients undergoing combined treatment with regard to invasiveness, follow-up, complications and cost/benefit ratio.

The patients were divided into 2 groups. In the 52 patients in group I, renal access from the lower calix led to more than 70% of the stone burden being removed by PCNL. In the 24 patients in group II the same procedure resulted in less than 70% of the stone burden being removed. There were no significant differences with regard to invasiveness, since the same renal access was used in both groups. Three months after treatment, 77% of the patients in group I were stone-free, compared with 83% in group II. Again, there were no significant differences between the groups. Complications are listed in Table 1. Their incidence was significantly higher in group II.

As far as the cost/benefit ratio was concerned, the differences listed in Table 2 were significant.

This retrospective study has allowed us to assess the type of staghorn calculi that can benefit from a combination of PCNL and ESWL. They comprise stones with most of their burden within the pelvis, more than 70% of which can be removed percutaneously. When this is not possible, as in group II, the percutaneous approach is not recommended because the residual stone burden does not justify

Table 1 Complications in Patients Treated with PCNL + ESWL

	Group I (PCNL > 70%)	Group II (PCNL < 70%)
Fever	50%	75%
Ureteric obstruction requiring URS	26%	25%
Bleeding	1.3%	3.9%
Renal haematoma	0	0

Table 2 Mean Cost/Benefit Ratio in Patients Treated with PCNL + ESWL

	Group I (PCNL > 70%)	Group II (PCNL < 70%)
Hospital stay	18 Days	25 Days
Shocks	2.3×10^3	5.2×10^3
ESWL sessions	1.5	2.5



Fig. 1 Plain X-ray of "not bulky" staghorn calculus.



Fig. 2 Plain X-ray of "pyelic bulky" staghorn calculus.



Fig. 3 Plain X-ray of "peripheral bulky" staghorn calculus.



Fig. 4 Plain X-ray of "giant" staghorn calculus.

an invasive procedure. In these cases an additional ESWL session can successfully replace PCNL. Alternatively, open surgery may be considered if the peripheral stone burden is excessive.

These results, when related to the new therapeutic procedures available for the treatment of urinary tract calculi, have led us to reappraise previous classifications of staghorn stones (Cukier, 1973; Moores and O'Boyle, 1976; Faure and Sarraon, 1982; Rocco *et al.*, 1984; Sigel *et al.*, 1986), based on morphological qualitative criteria compared with the surgical approach. We now tend to assess the morphological quantitative criteria (Di Silverio *et al.*, 1988) and so we have divided staghorn calculi into 4 groups according to the options currently available for their treatment:

Not bulky: thin, low density staghorn calculi entirely filling a small, non-dilated collecting system (Fig. 1).

Pyelic bulky: staghorn calculi with most of their burden in the pelvis; a small portion is present within the calices. Density appears quite high in the pyelic portion but decreases significantly in the caliceal portions (Fig. 2).

Peripheral bulky: staghorn calculi with most of their burden in the caliceal groups and a small portion in the pelvis. Density is quite high in the calices and the collecting system is consequently dilated (Fig. 3).

Giant: high density staghorn calculi with large pyelic and caliceal portions lying in a dilated collecting system (Fig. 4).

The therapeutic approach for each group is shown in Table 3.

Table 3 Classification and Treatment of Staghorn Calculi

Classification	Therapy
Not bulky	ESWL
Pyelic bulky	PCNL + ESWL
Peripheral bulky	Surgery or repeated ESWL
Giant	Surgery

We feel that this working classification will prove useful for any kind of staghorn calculi, provided it takes account of all therapeutic options available at present.

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Ureterovaginal Fistula: Summary of 18 Years' Experience

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Summary—Ureterovaginal fistula is an uncommon complication of pelvic operations. We report 31 such cases seen over an 18-year period, all of which followed surgery for benign gynaecological conditions. Most patients had no urinary symptoms until the sudden onset of incontinence 1 to 4 weeks post-operatively. Diagnosis was established by a combination of intravenous urography, cystography, cystoscopy, retrograde ureteropyelography and dye studies. Twenty-nine patients underwent ureteroneocystostomy, 10 with a Boari flap and 19 by a direct method; fistulas healed in 2 patients following conservative treatment. Renal salvage was achieved in all cases.

The course of the ureter in the retroperitoneum and its close proximity to the rectum and female reproductive organs in the pelvis render it particularly vulnerable to injury during vascular, gynaecological, urological and colonic surgery. The true incidence of iatrogenic ureteric injury is difficult to ascertain from the literature. Most studies review only those patients who require specialised urological intervention (Higgins, 1967). In most series, ureteric injury occurred in 0.5 and 1% of all pelvic operations (Mattingly and Borkowf, 1978) and in 2% of patients undergoing radical hysterectomy (Brown, 1977; Mattingly and Borkowf, 1978). Silent ureteric injury appears to be much more common. Mattsson (1975) and Ulmsten (1975) reported an incidence of 36 and 46% respectively following Wertheim's hysterectomy, using a combination of intravenous urography and isotope renography.

Ureterovaginal fistula, which occurs in 50% of patients requiring urological intervention (Higgins, 1967), is a serious sequela to ureteric injury, and its attendant incontinence causes great concern to both the patient and the surgeon.

Patients and Methods

From 1970 to 1988, 31 patients were referred for treatment of ureterovaginal fistulas. Their ages ranged from 23 to 55 years (mean 43.5). All fistulas occurred as complications of gynaecological operations (Table). No operation had been performed for malignant disease and no patient received prior radiation therapy. Only 3 patients reported mild flank pain that was referable to the urinary tract following the original operation. There was a delay of 5 to 28 days (mean 16) from surgery to the development of incontinence and the interval between the development of incontinence and referral to this clinic ranged from 2 days to several months. Three patients had coexistent large vesicovaginal fistulas; all had prolonged and difficult labour and required either emergency caesarian section or abdominal hysterectomy for the management of uterine rupture. Two patients had undergone ureteroneocystostomy for ureteric injury by the gynaecologist during the original operation and were referred to us because of the subsequent development of ureterovaginal fistula. Three patients had bilateral fistulas and in another 4 the fistula involved the solitary functioning renoureteric unit. All 7 of these patients had azotaemia

(serum creatinine 2–4.8 mg%) and resistant urosepsis. Exploration revealed pockets of pus in the pelvis in 6 of these patients.

An IVU demonstrated varying degrees of ureteropyelocaliectasis in 26 patients; the upper tracts were normal in the others. Six patients had poorly functioning kidneys on intravenous urography. Retrograde ureteropyelography demonstrated the fistula in 3 patients. The ureteric catheter could not be advanced beyond 1 to 6 cm from the ureteric orifice in 6 patients; the catheter entered the vagina in 2 and the orifice could not be identified at cystoscopy in the remainder. Dye studies were performed in 17 patients and all were positive.

One patient was treated expectantly as patency of the distal ureter was clearly visible on IVU. This fistula healed spontaneously in 3 weeks without complications. Temporary proximal diversion by a nephrostomy was carried out in 3 azotaemic patients to stabilise renal function and control urosepsis. In 1 patient the fistula healed following 6 weeks of nephrostomy drainage. Neither poor visualisation on IVU nor severe ureteropyelocaliectasis was regarded as an indication for nephrectomy in this series. Thus in all patients functional restoration was attempted. Ten patients underwent Boari flap replacement of the distal ureter and the remaining 19 had a direct ureteroneocystostomy. For bilateral fistulas 2 patients had bilateral Boari flaps fashioned, while the others underwent reconstruction by means of a transuretero-ureterostomy combined with a Boari flap. Patients with coexistent vesicovaginal and ureterovaginal fistulas were managed by O'Connor's repair with pedicled omental interposition and direct ureteroneocystostomy. A psoas hitch was used in 9 patients to ensure tension-free anastomosis. All ureteric reimplantations (either into the Boari flap or directly to the bladder) were made antireflux using the Politano-Leadbetter technique.

Table Operations Preceding the Onset of Ureterovaginal Fistula in 31 Patients

<i>Operation</i>	<i>No. of patients</i>
Total abdominal hysterectomy*	22
Vaginal hysterectomy	4
Repair of cystoectocoele	2
Caesarian section	3

*Two of these patients had undergone ureteroneocystostomy for ureteric injury during the original operation and subsequently developed ureterovaginal fistula.

Results

Of the 19 patients who underwent a direct ureteroneocystostomy, 2 had major complications: the distal ureter sloughed in 1 and ipsilateral renal function deteriorated after reimplantation in the other. Both underwent immediate re-exploration and renal salvage was achieved by Boari flap replacement of the distal ureter. No patient who underwent a Boari flap procedure had major complications. Wound infection prolonged post-operative recovery in 3 patients; 11 had positive urine cultures in the post-operative period but these cleared readily following appropriate antimicrobial therapy.

Follow-up ranged from 6 to 54 months (mean 24). During this period, urine cultures were sterile and renal function showed no deterioration once maximum recovery was achieved. Follow-up IVU at 3 to 6 months showed prompt function and good and symmetrical excretion on both sides. Residual mild pyelocaliectasis despite resolution of ureterectasis was seen in a few patients. No deterioration of renal function and urographic appearance was noted in these patients on subsequent follow-up. The patient in whom the fistula healed following nephrostomy drainage returned a year later with acute pyelonephritis. The infection was easily eradicated with antibiotic therapy and an IVU revealed no abnormality.

Post-operative cystography showed tenting of the bladder at the site of the psoas hitch and free reflux up the lower ureter in 3 patients.

Discussion

Trauma to the ureter during a surgical procedure occurs occasionally, even in the hands of the most experienced surgeon. Sims was reported to have ligated both ureters while demonstrating his operation for closure of a vesicovaginal fistula (Chassar Moir, 1961). Certain diseases of the reproductive organs, including endometriosis, pelvic inflammatory diseases and ovarian neoplasms, may distort the course of the distal ureter and thus make it particularly liable to injury. Approximately 80 to 90% of injuries occur in the distal portion of the ureter where it passes beneath the uterine vessels (Mattingly and Borkowf, 1978).

The increasing frequency with which carcinoma of the cervix is treated by radical (Wertheim's) hysterectomy, in which the terminal ureter is stripped of its fascial encasement in the broad ligament, has resulted in an increased incidence of

ureterovaginal fistulas (Lee and Symmonds, 1971; Mattingly and Borkowf, 1978; Goodwin and Scardino, 1980). Radiation therapy, either alone or as adjunct to surgery, is another important causative factor (Goodwin and Scardino, 1980). In the present series, all patients had undergone operations for benign gynaecological conditions. The coexistence of ureterovaginal and vesicovaginal fistulas is common. Lee and Symmonds (1971) and Goodwin and Scardino (1980) reported an incidence of 25 and 12% respectively of complex ureterovaginal and vesicovaginal fistulas.

Symptoms referable to the urinary tract during convalescence are mild and often undetected (Higgins, 1967). Symptoms were noted in only 3 of our patients before the onset of incontinence.

Diagnosis is straightforward in most cases. Varying degrees of ipsilateral ureteropyelo-caliectasis are frequently found on IVU, although the upper tracts may often be normal (4 patients in this series). Retrograde ureteropyelography and cystography should also be included in the evaluation of all patients. When transurethral and transvaginal catheterisation of the ureter fail, the upper tract may be demonstrated by an air vaginogram (de Shadarevian *et al.*, 1979). The presence of a fistula is readily confirmed by dye studies. Raghavaiah (1974) described an accurate method to localise fistulas. After careful packing of the vagina, red carmine is instilled into the bladder and indigo carmine is administered intravenously. Examination of the pack identifies the site of the fistula. The success of dye studies to confirm ureterovaginal fistulas depends on a satisfactory level of renal function (Higgins, 1967).

It has long been appreciated that immediate surgery in patients with ureterovaginal fistulas is not essential. The timing of surgical intervention depends on various factors, including the extent of the causative operation and the condition for which it was performed, the type and time of ureteric injury, the condition of the pelvic tissues and the general condition of the patient (Lee and Symmonds, 1971). Prolonged delay is seldom necessary or desirable (Goodwin and Scardino, 1980). If reconstruction is delayed, deterioration of the upper tract owing to stricture, which almost always accompanies a ureterovaginal fistula, may require early diversion. The incontinence causes distress and is difficult to relieve.

In a small number of patients the fistula may close spontaneously, either without any intervention or with the aid of an indwelling ureteric stent. In a study of 4 successfully treated patients, Hulse

et al. (1968) advocated conservative treatment when the injury was unilateral. However, of the 3 patients reported by Millin (1949), in whom the fistula closed spontaneously, 1 had stricture formation and underwent subsequent nephrectomy, while the remaining 2 required periodic dilatation for ureteric stricture. We recommended expectant treatment under close supervision in 1 of our patients as patency of the distal ureter was clearly visible on IVU.

Ureteroneocystostomy is the procedure of choice in most patients with ureterovaginal fistulas. Goodwin and Scardino (1980) advocated construction of an antireflux submucosal tunnel in all patients. All ureteroneocystostomies in the present series (either directly into the bladder or into the Boari flap) were accomplished using an antireflux technique by the Politano-Leadbetter method. To ensure a tension-free anastomosis, we prefer to fashion a Boari flap rather than rely on a psoas hitch alone. The other indication for raising a Boari flap was the finding of an abscess cavity in the pelvis, which allowed us to ensure a tension-free anastomosis far away from the infective focus.

Various operations have been reported in single cases or in small series; these include transuretero-ureterostomy combined with a Boari flap for bilateral injury (Weems, 1970), ileal replacement of lower ureter (Lee and Symmonds, 1971) and ileal conduit diversion (Higgins, 1967; Lee and Symmonds, 1971) and ileal conduit diversion (Higgins, 1967; Lee and Symmonds, 1971). Primary nephrectomy was done in 34 of 71 patients (48%) reported by Lee and Symmonds (1971), 24 of whom underwent surgery before 1958. Higgins (1967) reported a 22% incidence of primary nephrectomy, while Goodwin and Scardino (1980) reduced the nephrectomy rate to 5%. In our series all renal units were salvaged. In our experience nephrectomy should be considered as a last resort in the management of ureterovaginal fistula.

Acknowledgements

We are grateful to the past faculty and past and present residents of the Department of Urology and to the staff of the Central Registration Department, Postgraduate Institute of Medical Education and Research, Chandigarh.

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Application of the Invaginated Sleeve Technique to Form a Continent Ileal Urostomy

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Summary—The invaginated sleeve technique has been adapted to produce a continent urostomy, able to be catheterised, from a length of canine ileum measuring less than 10 cm. Of the 4 dogs catheterised twice daily up to 13 weeks, narrowing was present in the extra-ileal segment in 2, but all intra-ileal double-barrelled lumina remained healthy with preservation of bowel mucosa.

The construction of durable, continent stomas which are easy to catheterise remains a topic for careful consideration by urologists entertaining continent diversion. Stimulated by Kock's work, a number of techniques have been described (Kock *et al.*, 1978; Mitrofanoff, 1980; Handley Ashken, 1987; Koff *et al.*, 1987) but the ideal procedure continues to be sought.

Recently we described the development of a simple technique in dogs for fashioning a continent cystostomy (Gardiner and Samaratunga, 1989). This technique has been adapted in a short segment of canine ileum to enable formation of a continent ileal urostomy using the invaginated sleeve principle with omentum ensuring viability of the extra-ileal catheterising tract.

Patients and Methods

Six adult, female, cross bred dogs were used. Anaesthesia was induced with intravenous pentobarbitone (250–350 mg) and maintained with a fluorothane/nitrous oxide mixture following premedication with intravenous atropine (0.6 mg) and droperidol (1 mg/kg). An infusion of Hartmann's solution was administered intravenously per-operatively. Ampicillin (0.5 g intramuscularly) was given during the procedure and subsequently (0.5 g orally/day) continued as maintenance therapy.

All dogs underwent laparotomy via a midline incision. A segment of terminal ileum approximately 15 cm in length was isolated, the cut ends of the bowel being anastomosed to maintain gastrointestinal tract continuity. An index finger was placed in the proximal end of the isolated segment and, with cutting diathermy, a longitudinal cut was made through serosa and muscularis propria—but not deeper—on the anti-mesenteric aspect and this met the mid-point of a radial incision at the other end to produce a "T" appearance. With dissecting scissors, serosa and muscularis propria were dissected and then peeled back from the outer half of the diameter of the bowel lumen for the distance of the index finger (Fig. 1).

The exposed underlying bowel wall was then incised on both sides immediately adjacent to the edges of the retracted serosa and muscularis propria to form a pedicled graft of mucosa, lamina propria, muscularis mucosa and submucosa. The graft was tubularised around a fenestrated silastic stent with an outside diameter of 0.5 cm. Interrupted 5/0 dextron sutures were placed so that every second one was partly through the stent wall, fixing the graft to prevent any tendency to concertina and, at the same time, stretching so that the tubularised graft extended about 3 to 4 cm beyond the proximal end of the bowel segment (Fig. 2).

A tunnel was then fashioned by distracting tissues with small dissecting scissors. The tunnel commenced beneath the submucosa immediately

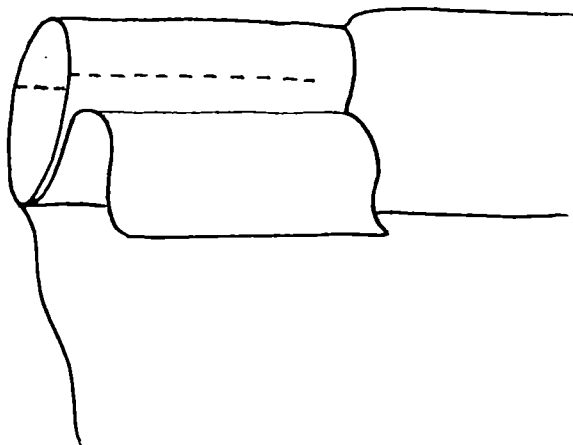


Fig. 1 Serosa and muscularis propria were stripped from the outer half of the proximal end of the bowel lumen.

adjacent to the mesentery at the proximal cut end of bowel and was advanced to the level of the pedicle of the graft. At this site, the mucosa was opened. The tunnel was enlarged so that a pair of de Bakey forceps could slide down beside the stent to grasp a length of dexion on the end suture to facilitate sliding of the graft through the tunnel (Fig. 3). Any graft tissue that had rolled over to form a lip was trimmed prior to passing the tubularised graft through the tunnel. The longitudinally opened bowel was sutured with continuous 4/0 dexion sutures to close the wall at the level of the peeled back serosa and muscularis propria and extended to the proximal end to create a "water-tight" closure.

Graft protruding beyond the bowel was wrapped with omentum and then brought out through a gap left between the rectus abdominis muscles (Fig. 3). This exit site was judged sufficiently spacious to

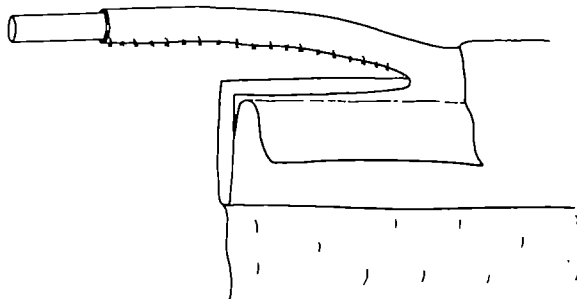


Fig. 2 Tubularisation of fenestrated Silastic stent.

allow viability of both graft and omentum but not herniation of other intra-abdominal structures. Protruding omentally wrapped graft was then placed in a space created just beneath the skin. After this manoeuvre, very little graft and omentum remained in the peritoneal cavity since several centimetres of tubularised graft were sited subcutaneously. The Silastic stent was clipped with Liga clips and folded on itself beneath the skin; the distal end of the bowel segment was spatulated slightly and then anastomosed to the opened bladder with 3/0 dexion sutures.

Dogs 1 and 2 were sacrificed 3 and 4 weeks respectively after the first operation with their stents in position. Dogs 3 to 6 had a second operation 2 weeks after the first, at which time the stents were removed and the graft ends were spatulated and anastomosed to skin. Dog 3 was catheterised twice daily for 10 days with an 8F disposable catheter; at that juncture resistance was encountered and further catheterisation was not attempted. Dog 5 was catheterised similarly for 7 weeks. Dogs 4 and 6 were catheterised daily with 8 and 12F catheters with little difficulty being encountered for 7 and 13 weeks respectively from their initial operations.

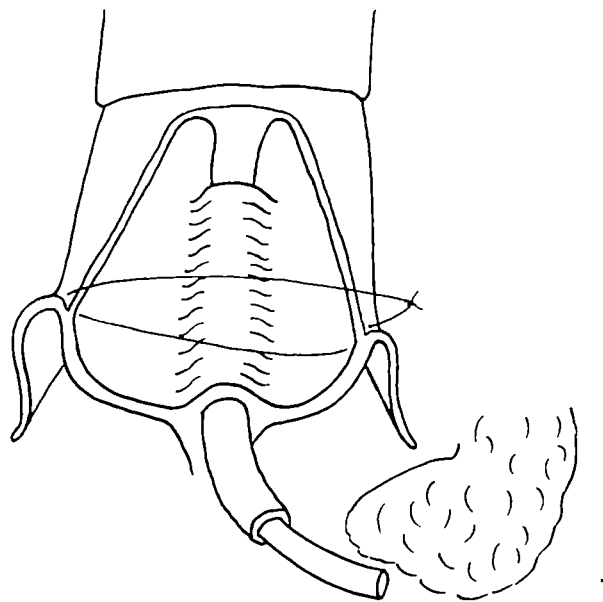


Fig. 3 Invagination of tubularised graft through submucosal tunnel. Cut ileal edges were sutured, forming double-barrelled lumina in this segment of bowel. Adjacent omentum was applied to protruding graft.

Urine was obtained per-operatively at the time of the second operation in dogs 3 to 6 and at the time of sacrificing. Specimens were examined microscopically and bacteriologically. Animals were sacrificed using intravenous pentobarbitone sodium (Lethobarb) 325 mg/ml. Macroscopic and histological examinations were made of the tunnels and catheterisation tracts. Tissues were fixed in formalin and paraffin embedded. Sections were stained with haematoxylin and eosin and haematoxylin van Gieson.

Results

The invaginated sleeve technique resulted in double-lumen tunnels in the bowel segments which were lined by ileal mucosa and surrounded by muscle which consisted of thin layers of smooth muscle of the muscularis mucosa type in the case of the grafts. The grafts were seen to be present in the submucosa of the proximal bowel segments (Figs 4 and 5).

The extra-ileal catheterisation tracts were lined partly by intestinal mucosa (Fig. 6) and, variably, by a single layer of cuboidal or columnar epithelium as well as epithelium resembling urothelium. Squamous metaplasia of the lining had taken place close to the distal end of the tract in dog 4. The extra-ileal tracts were surrounded by fibrous tissue in which were seen thin layers of smooth muscle which in turn were surrounded by supporting omental fatty tissue.

All of the 4 dogs catheterised twice daily for 10 days, 5 weeks, 7 weeks and 13 weeks from the second operation were continent. Little difficulty was encountered in passing the catheters in dogs 4 and 6, but in dogs 3 and 5 resistance was felt due to narrowing of the catheterising tracts sufficient to make passage of 8F catheters difficult. These were not forced and no attempt was made to use smaller catheters. Histological examination showed narrowed lumina with thickened walls of the extra-ileal part showing dense fibrosis. Urine specimens from all dogs—except dog 6—cultured positively for Gram-negative rods. *Escherichia coli* was identified from the urine of 4 of the other dogs, with urine from dog 5 culturing positively for *Pseudomonas aeruginosa*. None of the dogs had clinical urinary tract infection during the study period.

Discussion

Intussusception techniques involving ileum for continence mechanisms, such as that developed by

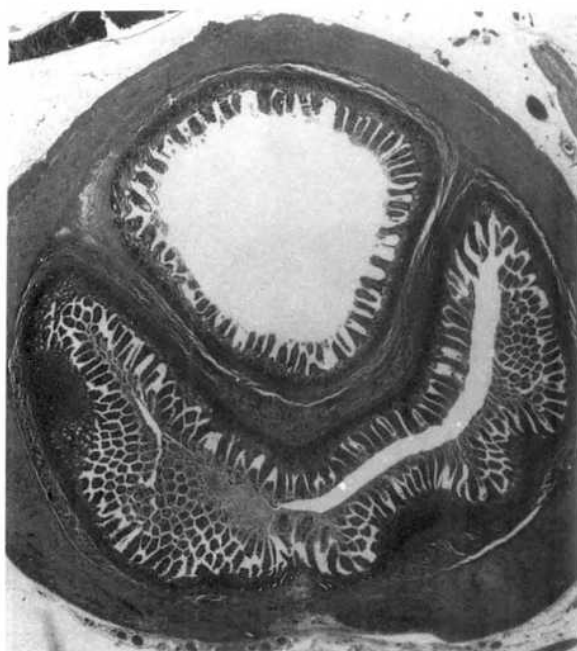


Fig. 4 Section through ileum showing a widely open catheterising tunnel, due to stent in position, lying in submucosa.

Kock, are extravagant in their use of bowel (Skinner *et al.*, 1987). A more frugal approach uses isolated appendix, ureter (in part or in continuity) or pedicled skin in an "anti-reflux" tunnel (Duckett and Snyder, 1986a and b; Gardiner, 1988; Mundy,



Fig. 5 Section through ileum with closed catheterising tract.

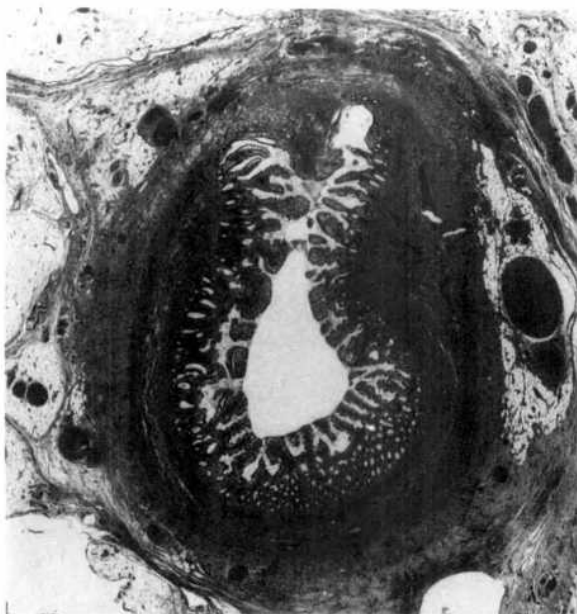


Fig. 6 Extra-ileal catheterising tract lined by bowel mucosa and supported by healthy omentum.

1988) variably dubbed, eponymously, the Mitrofanoff principle (Duckett and Snyder, 1986a and b). However, suitably pristine tissues may not be readily available to invoke this principle. Alternatively, ileal plication may be considered (Sarosdy *et al.*, 1987) and Bejany and Politano (1988) have described the use of 8 to 10 cm of ileum tubularised over a 14F catheter with "purse-string" sutures to create a segment of maximum pressure.

The invaginated sleeve technique uses an index finger's length of proximal ileum (<10 cm). The thinned pedicle graft stretches longitudinally and is fixed to the stent so that the resulting catheterising tract is >10 cm in length with a comparably small lumen. In addition, the catheterising tract has the extra advantage of a simply fashioned "anti-reflux" mechanism as a further barrier against loss of urine.

Viability of that part of the graft extending beyond the tunnel is provided by a generous wrapping of omentum, the benefits of which are well established in this context (Turner-Warwick, 1976; Samson and Pasternak, 1979; Gardiner *et al.*, 1984).

There is usually sufficient omentum after mobilisation to enable both ample covering and most appropriate siting of the catheterising tract and stoma. This thinner walled, omentally supported tube is supple, yet robust enough to permit regular passage of catheters. This functional ability is

consistent with histological findings in which muscle persists in this part of the graft (Fig. 6).

An interesting observation in these studies was the fact that bowel lining in the non-invaginated part of the tracts exposed to trauma by catheterising became metaplasted to a low cuboidal epithelium or replaced by transitional cell urothelium. Whether this would be so in the absence of an adjacent intact bladder in the non-experimental situation is conjectural, but a change in character of the mucosa of a catheterising tract might alter the effectiveness of a simple tube as a continent mechanism.

The tunnel beneath submucosa through which the graft was invaginated was formed by distracting tissues apart with dissecting scissors, commencing at the proximal end of the cut bowel immediately adjacent to the mesentery. The tunnel was continued to the level of the base of the pedicle graft. No difficulty was encountered with bleeding or "button-holing" with this manoeuvre. It is anticipated, however, that breaching the wall during this stage would not jeopardise formation of an "anti-reflux mechanism" since epithelium would probably cover the tubularised bowel wall sited in the resulting gutter in the same way that ureters develop a mucosal covering in the Le Duc procedure (Le Duc *et al.*, 1987).

Two catheterising tracts developed stenosis. In both dogs catheterisation was stopped when resistance was noted to 8 F catheters at 10 days and 7 weeks, although it is possible that a smaller size might have passed easily. In both instances the lumina of the omentally supported non-invaginated parts were reduced in diameter with increased fibrous tissue in the walls. It is unclear whether ischaemia or a consequence of trauma from catheterising (or both) was responsible for the stenoses. Another possibility is that the grafts were not made wide enough when they were applied around the stents at the time of surgery. The ileal grafts were not as supple as the grafts developed in the continent cystostomy experiments and did not stretch as readily, so an element of tension may have been present at the time of tubularisation. However, the times at which stenosis occurred, that stenosis was seen in only 2 instances and the tendency for narrowing to be mostly in the part of the grafts protruding beyond the bowel wall, suggest that this is, at best, only part of the explanation.

Although bacteriuria was the rule in these studies, 1 dog (number 6) had sterile cultures on 2 occasions. It was expected that bacteria would be present in urine in contact with bowel mucosa in these dogs and efforts were made to aspirate specimens for

culture from the ileal segments of the bladder-bowel combinations to avoid mistakes in sampling. Nevertheless, this might not have occurred. It is interesting that there was free communication between the bladders and anastomosed bowel segments with no evidence of narrowing at these sites. However, none of the dogs had any evidence clinically of urinary tract infection during the study period.

In conclusion, these studies have demonstrated that the invaginated sleeve technique is a simple procedure which uses only a short segment of ileum to produce a continent catheterising tract and stoma. The procedure requires careful dissection but offers an alternative technique for providing both a robust catheterising tract and a competent "anti-reflux" mechanism.

Acknowledgements

We are indebted to the staff of the Department of Surgery, University of Queensland, who cared for the animals and to the Pathology and Medical Illustration Departments at Royal Brisbane Hospital for their contributions to this study.

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Continence after Total Bladder Replacement: Urodynamic Analysis of the Ileal Neobladder

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Summary—Since April 1986 we have carried out 103 bladder substitutions with the ileal neobladder; 91 of these were performed after radical cystectomy in males (group 1) and 12 after subtotal bladder resection (group 2); 55 patients in group 1 and 8 in group 2 were followed up by long-term urodynamic investigations and by a questionnaire concerning micturition patterns and continence at home 3 months post-operatively. The maximum bladder capacity was approximately 770 ml with an absolute intravesical pressure of 23 to 30 cm H₂O. Intravesical pressure waves with a mean amplitude of 20 cm H₂O were found in 38% of patients in group 1 and 25% in group 2; 61% of these patients were asymptomatic.

The results showed that 85% of patients were continent by day and by night. We attribute this to our operative technique: the ileal loop is folded 4 times in a "W" or "M" shape to achieve complete detubularisation of the bowel and the external urethral sphincter is carefully preserved. Altogether, these data show the ileal neobladder technique to be a reliable and safe method of bladder substitution.

Over the last few years, urinary diversion after radical cystoprostatovesiculectomy has attracted great interest. Conduits and pouches with continent stomas are being replaced by total continent bladder substitution. The aim is to create a reservoir that imitates the behaviour of the normal bladder and provides continence both day and night without compromising the upper urinary tract. Significant progress was made by Kock (1969), who first constructed a continent low pressure bowel reservoir, and by Camey and Le Duc (1979), who first anastomosed ileum to the urethra. Modifications of these techniques incorporated their benefits and avoided the disadvantages of the Kock pouch and the Camey reservoir (Skinner *et al.*, 1984; Hautmann *et al.*, 1986, 1987, 1988; Light and Engelmann, 1986; Thüroff *et al.*, 1986; Melchior *et al.*, 1988). The aim of these modifications was 2-fold: firstly, to achieve a large capacity reservoir in order to avoid unacceptable frequency of micturition; secondly, to reduce pressure rises due to bowel

contractions, thus avoiding nocturnal incontinence. According to mathematical considerations (the capacity of a cylindrical reservoir increases with the square of the radius), the first goal is best achieved by generous folding of the bowel to produce a short, wide reservoir rather than a long, narrow one. The second goal is achieved by detubularisation of the bowel in order to avoid contractions encompassing the entire circumference.

With these aims in mind, the technique of the ileal neobladder was developed at this institution in April 1986. We present the geometric rationale behind the surgical technique together with the urodynamic results.

Patients and Methods

Between April 1986 and January 1989, we created 103 ileal neobladders: 91 in men with invasive or multifocal bladder cancer as total bladder substitution after radical cystoprostatectomy (group 1), and 12 bladder augmentations after subtotal bladder

resection in patients with shrunken bladders (group 2) (Table 1). The operative technique has been described in detail by Hautmann *et al.* (1987, 1988) and Egghart *et al.* (1988). Fifty-five patients in group 1 and 8 patients in group 2, who had been followed up for a minimum of 3 months post-operatively, underwent urodynamic investigation (Urocompact 8 000, Fa. Wiest, West Germany). Measurements were made with a 10 F multichannel catheter and contrast medium at an inflow rate of 50 ml/min, with the patient in the supine position. Maximum bladder capacity and absolute intravesical pressure were measured; mictiometry, EMG and cystography were also performed. The absolute intravesical pressure was assessed at maximum bladder capacity over a 30-min period in order to detect pressure waves generated by peristalsis of

the bowel. In addition to urodynamic data, a questionnaire was used to evaluate the patients' voiding patterns and continence at home.

Results

The results of the urodynamic investigations, including mictiometry, are shown in Table 2. Typical cystomanometric and urethral pressure profiles are shown in Figures 1 to 4. Intravesical pressure waves during cystomanometry, which were noted in 23 patients (37%), occurred in 14 patients (61%) only at maximum bladder capacity and in 6 (26%) at half maximum capacity. Only in 3 patients (13%) were the pressure waves observed at below half maximum bladder capacity. Mild nocturnal incontinence occurred in 2 patients and mild stress incontinence by day in 2 patients in group 1. Two patients achieved continence at night by using an alarm clock to ensure regular bladder emptying. The 2 patients with intravesical pressure oscillation after bladder augmentation were continent by day and night. In the other 14 patients the pressure waves did not cause incontinence. Mictiometry showed that the mean residual urine was below 50 ml. Only 1 patient was readmitted with overflow incontinence. After several days of intermittent catheterisation, together with short (4 h)

Table 1 Indications for Bladder Augmentation in 12 Patients

	<i>No. of patients</i>
Tuberculosis	5
Interstitial cystitis	3
Pelvic irradiation	2
Undiversion of ileal conduit (neurogenic bladder)	2

Table 2 Results of Urodynamic Examination of the Ileal Bladder (including mictiometry) after Radical Cystoprostatectomy (n = 55) and Subtotal Bladder Resection (n = 8)

	<i>Total bladder replacement (range)</i>	<i>Bladder augmentation (range)</i>
Maximum bladder capacity (ml)	768 (330–2000)	775 (350–1500)
Absolute intravesical pressure (cm H ₂ O)		
At half maximum capacity	12.3 (0–27)	11.5 (3–32)
At maximum capacity	30 (13–44)	23 (14–35)
Intravesical pressure waves (cm H ₂ O)	20 (10–60) in 21 patients	25 (20–35) in 2 patients
Micturition by abdominal straining (cm H ₂ O)	71 (20–150)	56 (40–100)
Mictiometry		
Single micturition volume (ml)	722 (221–1690)	628 (222–1520)
Micturition time (s)	93 (10–360)	50 (15–180)
Maximum flow (ml/s)	25.5 (5–50)	33 (20–49)
Mean flow (ml/s)	15 (2–40)	17 (8–39)
Residual urine (ml)	18 (0–600)	Nil (3 patients carry out intermittent catheterisation)
Vesicoureteric reflux (RUU)	4	2
Maximum urethral closure pressure (cm H ₂ O)	50 (10–90)	70 (28–188)

Table 3 Micturition Patterns at Home

	Group 1 (range)	Group 2 (range)
Diurnal frequency	5.9 (3–9)	6 (5–8)
Nocturnal frequency	1.1 (0–3)	0.8 (0–2)
Single micturition volume (ml)	360 (193–646)	334 (126–775)
Sterile intermittent catheterisation		3

voiding intervals, he was able to empty his bladder completely. A symptomatic urinary tract infection with fever required treatment in 1 patient. In Figure 5 the cystogram shows a typical form of the ileal neobladder, with no reflux. Vesicoureteric reflux was seen in only 4 reno-ureteric units (RUU) in group 1 and 2 in group 2. Reflux occurred in 4 of these units after undiversion of an ileum conduit. In 1 patient, pre-operative reflux disappeared after bladder augmentation. The micturition patterns seen at home are shown in Table 3. Continence by day and by night was achieved in 65/77 patients (85%); 3 patients (4%) were continent by day, but needed 1 pad or a condom at night. Mild stress incontinence, with occasional loss of urine but requiring no specific therapy (1–2 pads per day) occurred in only 5 patients as a result of weak external sphincter function. Four other patients had moderate or severe stress incontinence. One female patient in this group was severely incontinent after bladder augmentation following radiotherapy, but unchanged compared with the preoperative status. There were no pressure rises with the ileal neobladder in these patients during urodynamic evaluation (Table 4).

Table 4 Continence Rate of Patients with Ileal Neobladder

	Total bladder replacement (%)	Bladder augmentation (%)	Total (%)
Total continence day and night	56 (85)	9 (82)	65 (85)
Continent by day, pad or condom at night	3 (4)		3 (4)
Stress incontinence			
Mild (no pads)	4 (6)	1 (9)	5 (6)
Moderate	1 (2)		1 (1)
Severe	2 (3)	1 (already preop. 9)	2/1 (3/1)
Totals	66 (100)	11 (100)	77 (100)

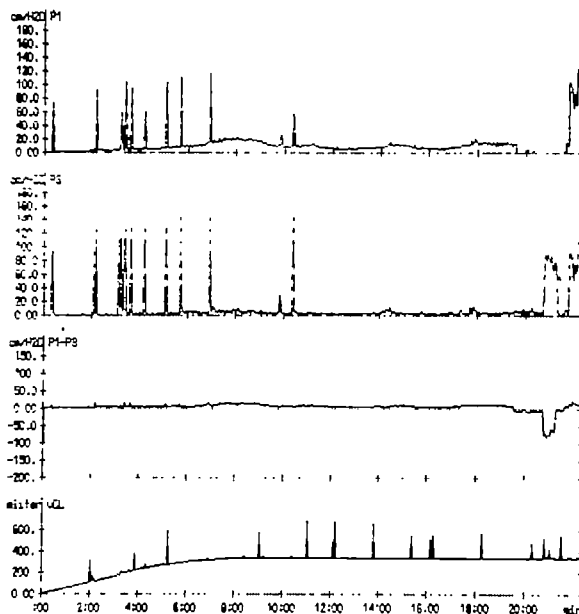


Fig. 1 Urodynamic examination of total bladder substitute after radical cystoprostatectomy: constant low intravesical pressure without pressure waves. P_1 =intravesical pressure, P_3 =intra-abdominal pressure, P_1-P_3 =differential pressure, vol=volume.

Stricture of the urethra as a late post-operative complication was found in 10 patients. In 2 cases the strictures were dilated as they were immediately adjacent to the external sphincter. In the remainder the strictures were incised by optical urethrotomy.

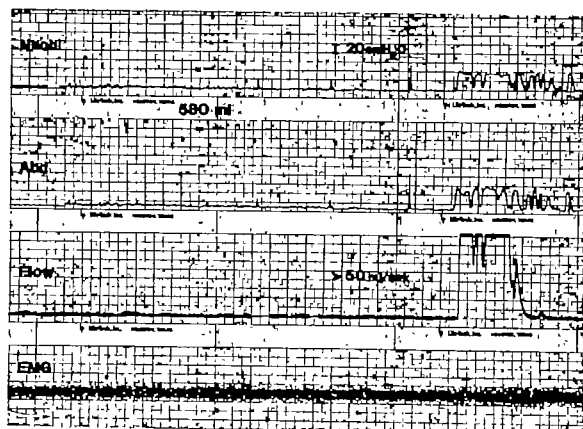


Fig. 2 Urodynamic investigation of ileal neobladder after bladder augmentation: at maximum bladder capacity of 580 ml the intravesical pressure is stable, micturition by abdominal straining with a maximum flow > 50 ml/s. Neobl. = intravesical pressure. Abd. = intra-abdominal pressure.

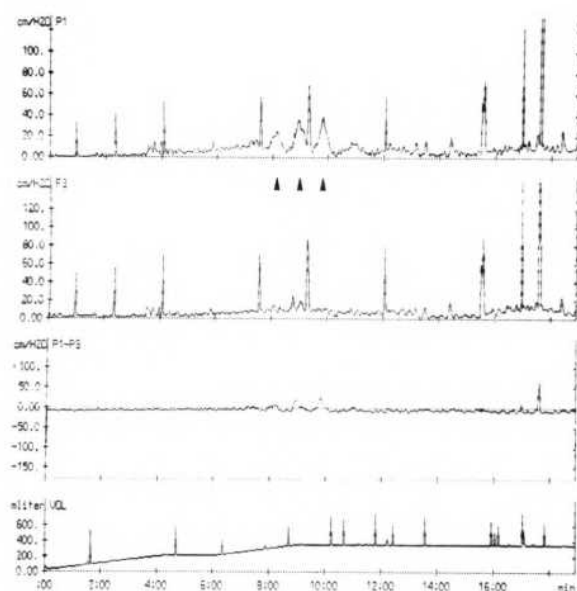


Fig. 3 Intravesical pressure waves up to 40 cm H₂O (arrows) with differential pressure of 20 cm H₂O in a patient after total bladder substitution. P₁=intravesical pressure. P₃=intra-abdominal pressure. P₁-P₃=differential pressure. vol=volume.

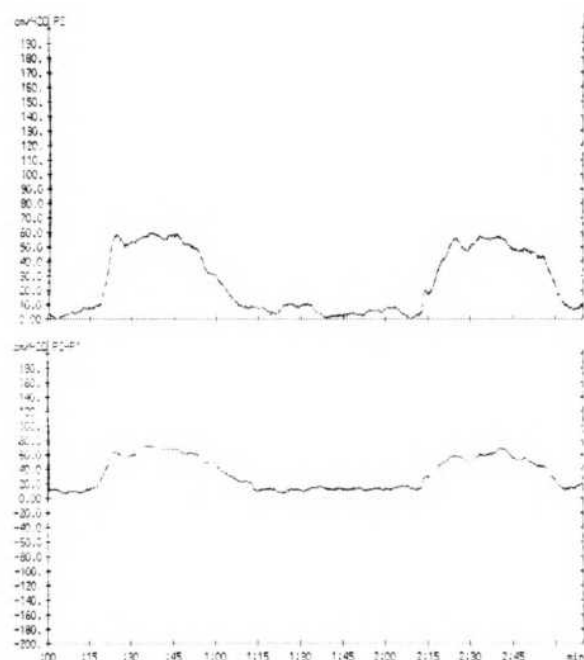


Fig. 4 Urethral pressure profile after total bladder replacement: reproducible maximum urethral closure pressure 60 cm H₂O.

Discussion

The aim of total bladder substitution by an intestinal reservoir is to imitate normal bladder function. The volume of a cylindrical bowel segment is determined by the formula: $V = \pi \cdot r^2 \cdot h$, where V is volume, r is radius and h is length (Hinman, 1988). As volume increases by the square of the radius, the radius is the most important factor in reservoir capacity. This is the rationale behind construction of the ileal neobladder: by detubularisation and folding of the intestine the volume can be increased 4-fold. Moreover, detubularisation abolishes synchronous intestinal contractions. Peristalsis that does not encompass the entire circumference occurs occasionally with only low intra-luminal pressure rises (Hinman, 1988).

The capacity of the neobladder is comparable to that of the normal bladder. Thus the micturition observed at home were not markedly different from those seen during the pre-operative period. In patients with shrunken bladders following repeated TUR, irradiation, tuberculosis or interstitial cystitis, the frequency returned to normal. Only 3 patients required intermittent sterile catheterisation after bladder augmentation, due to high residual urine volumes.



Fig. 5 Cystogram showing typical shape of the ileal neobladder: no reflux is seen.

As a result of the high compliance, low intravesical pressures (25 cm H₂O) were found in the neobladder at maximum bladder capacity. Together with a reliable antireflux and antiobstructive ureteric implantation technique, the low pressure protects the upper urinary tract (Le Duc *et al.*, 1987).

Another problem with total bladder replacement by bowel reservoirs is nocturnal incontinence due to bowel contractions. In this situation, the intrinsic pressure supersedes the closure pressure of the external sphincter and this is reduced at night. In the present series, 85% of patients were continent

by day and night. This proves the theory that complete detubularisation plus folding of the bowel 4 times desynchronises bowel contractions, thus avoiding significant pressure rises and enuresis in most cases.

In conclusion, the ileal neobladder meets the requirements for a continent bladder substitute. Folding and total detubularisation of the ileal loop mean that a bowel segment of only 60 cm is needed to achieve a good capacity reservoir with low intravesical pressure (Figs 6 and 7). These urodynamic properties protect the upper urinary tract and result in a high rate of continence. The ileal neobladder is a reliable, effective and safe method of total bladder replacement from a mathematical, medical, psychological and social point of view.

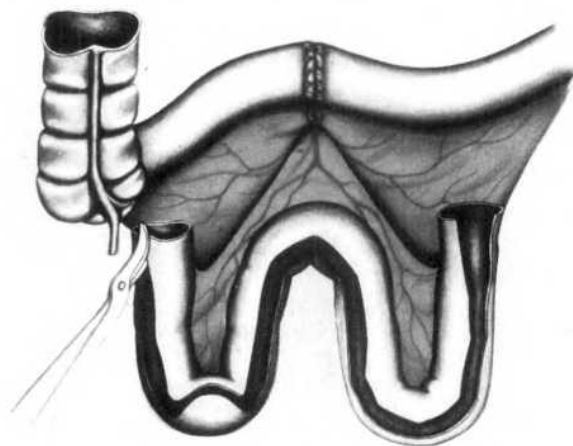


Fig. 6 Folding the terminal ileal loop 4 times and detubularisation.

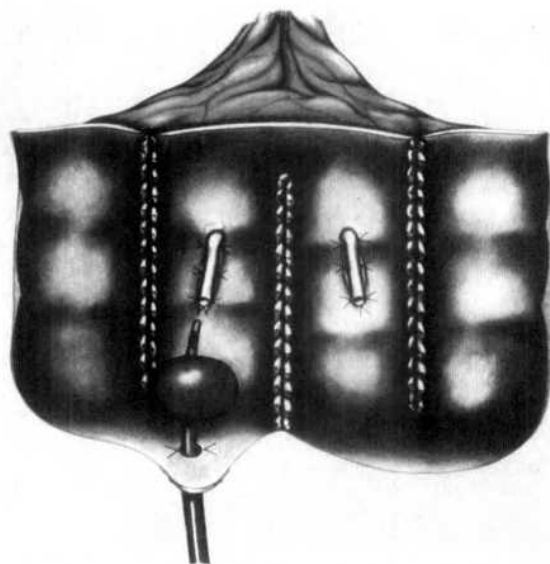


Fig. 7 Ileal neobladder before closure after anastomosis to the urethra and implantation of the ureters.

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Total Bladder Replacement in the Male and Female Using the Ileocolonic Segment (LeBag)

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Summary—A group of 11 patients, 2 female and 9 male, underwent total bladder replacement using the ileocolonic segment (LeBag technique) with anastomosis of the bowel to the urethra. The diagnosis was invasive bladder cancer in 10 patients and severe intractable interstitial cystitis in 1. The surgical technique in the male patients was modified to simplify the procedure. The 2 female patients underwent insertion of an artificial sphincter around the bowel segment for a continence mechanism. One patient died 6 weeks post-operatively from a severe coagulopathy. Five of the 9 male patients are continent day and night, relying on their own residual sphincter mechanism, but the remaining 4 required insertion of the artificial urinary sphincter to achieve social continence. The surviving female patient is totally continent. All patients have voiding intervals of 4 to 6 h during the day and are thus continent both day and night, but in some cases the artificial sphincter was necessary to achieve this. Loss of the normal bladder-sphincter reflexes following cystectomy may account for the high incidence of nocturnal incontinence observed in most series. Total bladder replacement is now possible in both male and female patients, thus avoiding an abdominal stoma.

Conventional management of the urinary tract following cystectomy has been the ileal or colonic conduit urinary diversion. This, however, requires an external collecting device with all the associated problems well known to urologists. More recently, the construction of a continent urinary diversion pioneered by Kock has eliminated the necessity for a bag (Kock *et al.*, 1978). Although regular intermittent catheterisation is required to drain the pouch, this has significantly improved the quality of life in these patients when compared with the ileal loop. Anastomosis of a neobladder to the urethra would represent a further refinement in the continuous evolution of lower urinary tract reconstruction as this would avoid an abdominal stoma while allowing for normal urination. This series is an update on the use of the LeBag technique previously reported in males where the ileocolonic segment is anastomosed to the urethra (Light and Engelmann, 1986). In addition, the use of this operation in females is reported.

Patients and Methods

Eleven patients, 2 female and 9 male, underwent total bladder replacement using the LeBag technique with anastomosis of the bowel to a urethral remnant. Their ages ranged from 40 to 76 years (mean 67). The diagnosis was invasive bladder cancer in 10 and severe intractable interstitial cystitis in 1. All 9 male patients with bladder cancer underwent a radical cystectomy. In both female patients, a small trigonal remnant was used for the bowel-urethral anastomosis.

The technique used to reconstruct the LeBag was similar to that reported previously with some minor modifications. In essence, 20 cm of ascending colon and an equivalent length of distal ileum are isolated on a common vascular pedicle, the ileocaecal artery (Fig. 1A). Both the large and small bowel segments are then split along the entire antimesenteric border to create 2 flat sheets (Fig. 1B). The ileal tail previously described has thus been eliminated (Fig. 1C). In the 2 female patients, however, 4 cm of distal ascending colon were maintained in the tubularised form for anastomosis to the trigonal

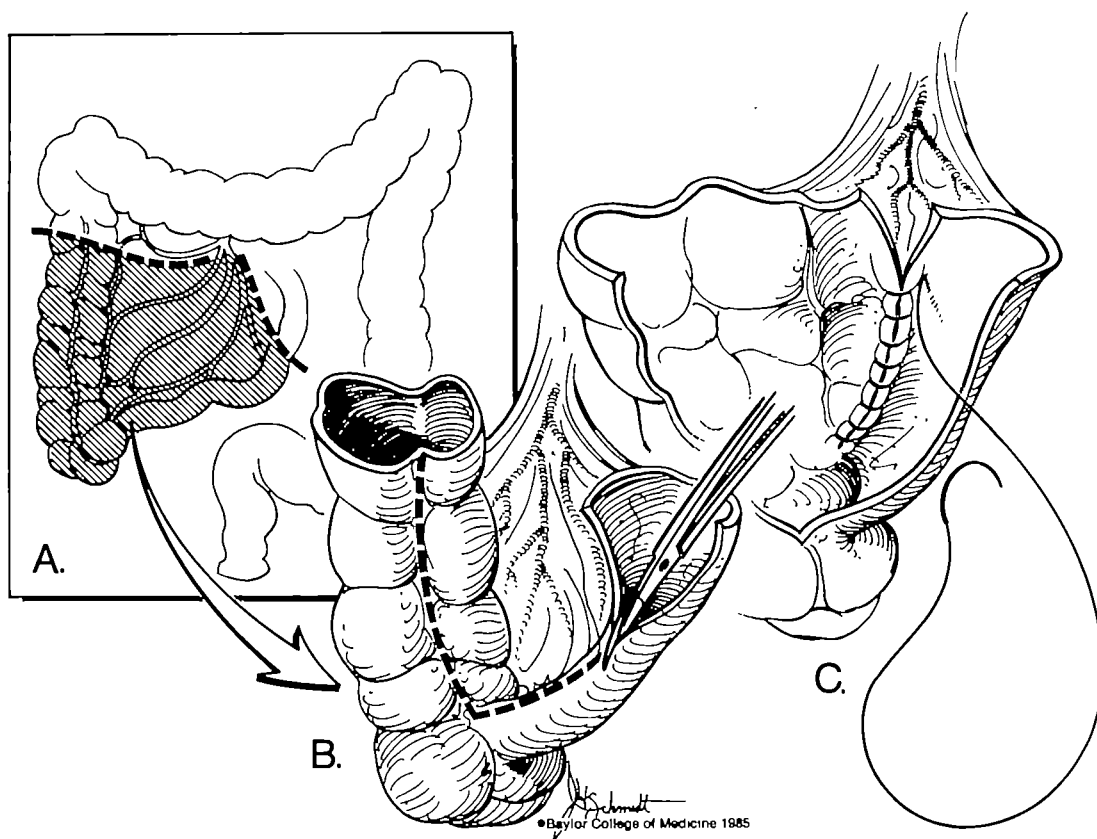


Fig. 1 (A) The ileocolonic segment to be used for the bladder replacement is illustrated. The vascular supply is the ileocaecal artery. (B) The ileocolonic segment is incised along the antimesenteric border completely to create 2 flat sheets of bowel. (C) The posterior wall of the pouch is being created. Note the absence of the previously described tubularised ileal tail.

remnant and for placement of the cuff from the artificial urinary sphincter (Fig. 2). The pouch is formed by stapling the 2 segments of bowel together, taking care to place the staples only on the serosal side of the bowel. No staples therefore entered the luminal aspect of the pouch.

In the male patients, the pouch is then slid down to the pelvis and the urethra anastomosed end-to-side to the caecum (Fig. 3). This eliminates the 180° rotation previously described to anastomose the ileal tail to the urethra.

In the 2 female patients, rotation of the pouch is necessary in order to place the tubularised portion of colon in juxtaposition to the urethral remnant or vagina for anastomosis. Both ureters are then implanted into the colonic portion of the pouch as previously described using the Goodwin intraluminal technique (Goodwin *et al.*, 1953). The cuff is placed precisely at the junction between the tubularised colon and inferior portion of the pouch

(Fig. 4). Ureteric stents are not routinely used. A 22 F Foley catheter is placed *per urethram* and sutured in position.

No patient had histological evidence of carcinoma *in situ*, tumour or epithelial dysplasia involving the bladder neck or prostatic fossa.

The patients underwent intravenous urography and urodynamic evaluation with simultaneous fluoroscopy 3 months post-operatively and then annually. Serum electrolytes were measured at the same time interval. A determination was made as to continence at each visit. Social continence was defined as being totally dry or not requiring more than 1 pad/24 h with voiding intervals of 4 to 6 h.

Pelvic floor electromyography using a concentric needle placed percutaneously into the periurethral muscle was performed in 3 incontinent male patients during the urodynamic evaluation. The results were recorded on a Disa 1500 electromyograph.

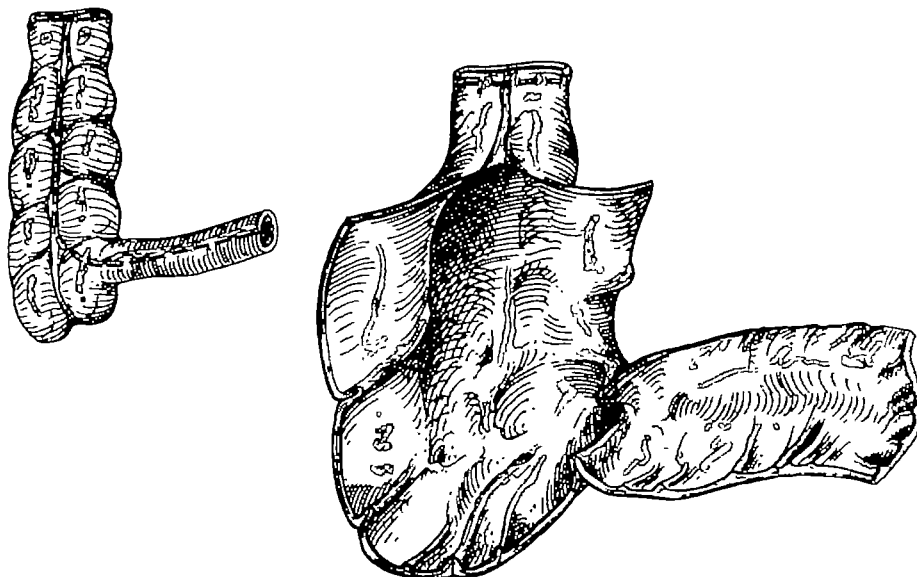


Fig. 2 In the female patient, the distal 4 cm of the colonic portion of the ileocolonic segment is maintained in a tubularised form. The ileocolonic pouch is then constructed in an identical manner to that in the male.

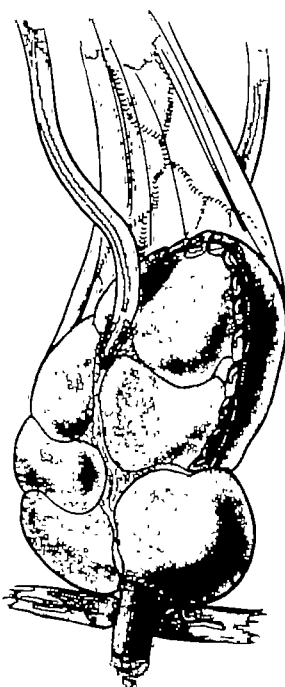


Fig. 3 The completed ileocolonic pouch in the male with end-to-side anastomosis of the urethra to the caecum.

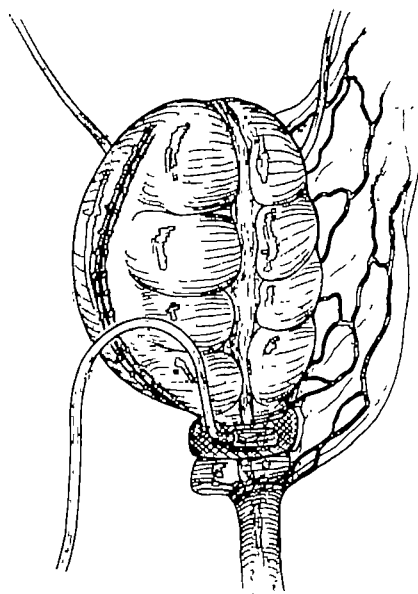


Fig. 4 The completed ileocolonic pouch in the female with anastomosis of the tubularised colonic portion to the urethra. Note that the cuff has been placed precisely at the junction between the pouch and the tubularised segment. The colon could be anastomosed to either the vaginal introitus or anterior vaginal wall if a urethrectomy has been performed.

Results

One patient (female with interstitial cystitis) died 6 weeks post-operatively after a complicated course initiated by the development of a severe coagulopathy. This eventually resulted in multi-organ failure and death.

The follow-up period of the remaining 10 patients ranged from 6 to 52 months (mean 36.5).

Eight patients are voiding satisfactorily *per urethram* using abdominal straining, with adequate emptying of the pouch. Two male patients perform self-intermittent catheterisation as they have been unable to learn the technique of abdominal straining with simultaneous relaxation of the pelvic floor.

Five of the 9 male patients are continent day and night as their residual distal sphincteric mechanism is adequate. The remaining 4 underwent insertion of the artificial urinary sphincter because incontinence persisted after 4 months. The cuff was placed around the bulbar urethra. All are now continent day and night with voiding intervals of 4 to 6 h during the day and no nocturia. The 1 female patient is also continent, voiding *per urethram* every 4 to 6 h.

An anastomotic stricture occurred between the ileal tail and urethra in 2 patients, 1 of whom had undergone previous pelvic irradiation. Both required endoscopic surgery.

Two patients developed symptomatic urinary tract infections following surgery and required antibiotic treatment.

The intravenous urogram revealed normal upper tracts in all patients 1 year post-operatively, although initial mild ureteric dilatation was noted in some patients at 3 months.

No patient developed persistent diarrhoea as a result of the surgery. Serum electrolytes, particularly the chloride and carbon dioxide, have remained normal in all patients.

Urodynamic evaluation at 3 months revealed a mean pouch capacity of 620 ml (range 500–760). Low amplitude contractions were observed in some patients but were of short duration and more obvious at pouch capacity. The pressure of these contractions at capacity ranged from 20 to 58 cm of water (mean 40). No ureteric reflux was observed on fluoroscopy. Bowel contractions were, however, frequently visible but were not associated with any intraluminal pressure increase. Fluoroscopy during voiding in the earlier cases showed some distortion of the ileal tail with abdominal straining, probably accounting for the lower peak flow rates in 2 patients. The remaining 7 patients all have excellent flow rates.

The use of staples to form the pouch significantly decreased the surgery time. No complications such as migration of the staples into the lumen, calculus formation or urinary leak occurred.

No evidence of periurethral muscle denervation was found in the 3 incontinent male patients in that positive sharp waves, fibrillation of potentials and increase in the number of polyphasic motor unit potentials were not observed. In addition, the basic tonic activity of this muscle did not change with progressive filling of the neobladder. Coughing and volitional contraction, however, produced a full interference pattern.

Discussion

Numerous bowel segments have recently been used to construct a neobladder and include ileum, ascending and sigmoid colon, and the ileocaecal segments (Goldwasser *et al.*, 1986; Webster and Bertram, 1986; Melchior *et al.*, 1988; Studer *et al.*, 1989). As shown by Light and Engelmann (1985) and recently emphasised by Hinman (1988), detubularisation of the bowel segment is essential to achieve a low pressure, compliant storage organ. All of the above bowel segments, when detubularised, appear capable of forming a low pressure neobladder.

Anastomosis of this neobladder to the urethra, however, is relatively new. Candidates must not have any evidence of carcinoma *in situ* or epithelial dysplasia involving the bladder neck in both sexes and also the prostatic fossa in males. The crucial factor is the continent status of the patient following this procedure. While 5 of the 9 male patients in this series were considered to be socially continent, the other 4 experienced varying degrees of incontinence. Incontinence at night was generally worse than during the day. Urodynamic evaluation revealed sphincteric weakness in these 4 patients and an artificial urinary sphincter was implanted with the cuff being placed around the bulbar urethra. All 9 male patients now have social continence and, equally important, void or catheterise only 4 to 5 times every 24 h. Thus continence has not been achieved at the expense of diurnal or nocturnal frequency.

Other reports have indicated acceptable daytime continence but troublesome incontinence during sleep, a fact also observed in some patients in this series. Melchior *et al.* (1988), using detubularised ileum, reported excellent daytime continence in 21 patients, some of whom were followed up for more than 9 months (Melchior *et al.*, 1988). Several

patients, however, had troublesome nocturnal incontinence. Reddy and Lange (1987), using the sigmoid colon, reported all 10 patients incontinent at night, although 8 were continent during the day. Ghoneim *et al.* (1987) used a hemi-Kock pouch anastomosed to the urethra in 16 patients. With a follow-up period of 3 to 9 months, all attained daytime continence but again nocturnal enuresis occurred in 4 cases, with 3 responding favourably to vasopressin medication.

The nocturnal incontinence that occurs in some patients may be secondary to 1 or more factors. A pseudodiuresis was observed by Melchior *et al.* (1988) due to the excretion of acidic urine. This resulted in a large volume of water being secreted by the ileal mucosa, causing overflow incontinence. The addition of citrate in the evening neutralised the acidic urine, thus decreasing the amount of water secreted by the ileum and improving the incontinence. The addition of vasopressin by Ghoneim *et al.* (1987) presumably decreased the nocturnal renal output, improving the nocturnal incontinence. It is difficult to understand how this treatment worked, since the vasopressin would not affect the reaction between concentrated urine and ileal mucosa. The increased nocturnal urine output was not observed in this series. The use of a different bowel segment, ileal versus ileocolonic, may explain this.

Relative weakness of the residual sphincteric mechanism may occur secondary to surgical damage or the loss of certain bladder-sphincter reflexes. As daytime continence has been excellent in virtually all of the reports from various centres, it appears unlikely that surgical damage to the residual sphincteric mechanism is the main cause of nocturnal incontinence. With an intact nerve supply, there is normally an increase in sphincter activity with bladder filling, thus increasing the urethral closing pressure. The main reflex arc involved is pelvic nerve afferent to pudendal nerve efferent acting through the sacral segmental interneurons. Other spinal reflexes may also be involved. In addition, the local vesicourethral reflexes may affect sphincter tone. These are obviously lost following radical cystectomy and substitution of the bladder with bowel. The inability of the sphincteric mechanism to respond reflexly with increased activity to volume changes in the neobladder could result in relative sphincter incompetence with leakage.

All 3 patients who underwent electromyography had loss of this reflex as there was no increase in the tonic muscle activity even at capacity of the

neobladder. In addition, no evidence of denervation was found to account for the sphincteric weakness. This relative sphincteric weakness would be more prone to occur during the night, when the urethral closing pressure decreases significantly secondary to an overall decrease in striated muscle tone. The postural reflexes, however, which involve the pudendal nerve and descending spinal cord tracts, would remain intact. Assuming an upright posture would still result in the normal reflex increase in pelvic floor muscle activity, including the striated muscle component of the distal sphincteric mechanism, this would explain why continence during the day is achieved earlier than at night.

The recruitment of motor units with coughing and volitional contraction is dependent on the descending spinal cord tracts and pudendal nerve being intact. Again, all 3 patients demonstrated normal responses to these manoeuvres, indicating that these reflexes and their pathways were intact.

The return of daytime continence first was observed in the 5 male patients who did not require insertion of the artificial sphincter. It has been clearly shown that the pressure generated by an intact bowel segment can overcome the residual natural sphincteric mechanism at night (Jakobsen *et al.*, 1987). This is due to a combination of the pressure exerted by the bowel segment and the physiological decrease in the closing sphincteric pressure. In addition, the bowel contractions can exert sufficient pressure to overcome the artificial urinary sphincter (Light and Scott, 1984); hence the importance of disrupting the directional peristalsis of the bowel segment used to replace the bladder.

A degree of nocturnal incontinence may be inevitable if loss of the pelvic-pudendal reflex is important. The artificial urinary sphincter, however, was used successfully in this series to restore continence from sphincteric weakness irrespective of the cause.

The female patient undergoing cystectomy has previously been managed with a supravescical diversion, either continent or incontinent. Encouraged by the previous success of using the cuff around bowel with total bladder replacement, this concept was extended to the female patients undergoing radical cystectomy for invasive bladder cancer (Light and Scott, 1984). The female patient in this series has done extremely well following combined use of the LeBag procedure and the artificial urinary sphincter. She is totally continent with voiding intervals of 4 to 6 h and experiences a normal sexual life. Use of the artificial urinary

sphincter around bowel is a viable concept provided infection does not occur and the balloon pressure does not exceed the bowel capillary perfusion pressure. Previous animal and human experience has shown this pressure to be 80 cm of water (Engelmann *et al.*, 1985; Light, 1989). In this patient and in those reported previously, the balloon pressure did not exceed 70 cm of water. The longest follow-up in humans with the cuff around bowel is now 11 years (Light, 1989).

The bowel may be anastomosed to a urethral remnant in female patients requiring simple cystectomy or the vaginal vestibule if urethrectomy is necessary, as in diffuse carcinoma *in situ* or invasive bladder cancer. Two of the 3 female patients previously reported have undergone anastomosis to the anterior vaginal wall and the 2 in this series to a trigonal remnant.

The LeBag procedure with anastomosis to the urethra or anterior vaginal wall has been used successfully to form a neobladder in both male and female patients undergoing cystectomy. This has resulted in normal urination. If reconstructive surgery alone fails to result in satisfactory continence in the male, placement of the artificial urinary sphincter around the bulbar urethra will achieve social continence. Use of the artificial urinary sphincter around bowel gives female patients the option of similarly achieving normal urinary and sexual function, thus avoiding an abdominal stoma and the need to perform intermittent self-catheterisation.

Careful pre-operative evaluation, both medical and psychological, is required to determine whether the patient is a suitable candidate for this type of reconstruction.

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Treatment of Bladder Carcinoma Using a Germ Cell Chemotherapy Protocol

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Summary—Elevated levels of circulating β -human chorionic gonadotrophin (β -HCG) are commonly associated with a variety of tumours of germ cell origin. Other carcinomas may possess choriocarcinomatous elements but only rarely have there been reports of transitional cell carcinomas of the bladder associated with raised germ cell tumour markers, possibly because assays are not routinely performed.

We present 3 patients with advanced transitional cell carcinoma of the bladder, 2 with metastatic and 1 with locally invasive disease, who had raised levels of germ cell tumour markers. These patients were therefore treated with combination chemotherapy appropriate to such tumours, with excellent results, as shown by clinical improvement and return to normal of tumour marker levels. Recent reports of the association between bladder carcinoma and ectopic synthesis of β -HCG are reviewed. It was concluded that the production of β -HCG is probably not rare, but that when it is found, the adoption of an appropriate chemotherapeutic regime may be successful.

It is well established that increased levels of circulating β -human chorionic gonadotrophin may be associated with a variety of tumours of trophoblastic origin, in both men and non-pregnant women.

The assay of urinary and serum β -HCG has provided a means of monitoring the progress of treatment in cases of choriocarcinoma and testicular cancer with choriocarcinomatous elements for over 50 years. Other carcinomas may feature choriocarcinomatous elements, including tumours of the stomach (Regan and Cremin, 1960), lung (Dailey and Marcuse, 1969) and oesophagus (McKechnie and Fechner, 1971), but it is unusual for transitional cell carcinoma of the bladder to be associated with elevated serum levels of β -HCG (Kawamura *et al.*, 1978).

By February 1986 only 11 cases of primary choriocarcinoma of the bladder had been reported (Shah *et al.*, 1986) and only 3 documented cases of transitional cell carcinoma with gonadotrophin

secretion (Civantos and Rywlin, 1972; Kawamura *et al.*, 1978). However, subsequent immunohistochemical investigation of 13 other bladder carcinomas revealed β -HCG-like immunoreactivity in 5, which would suggest that this property is not as rare as was previously supposed (Rodenburg *et al.*, 1985).

Indeed, in a review of 104 transitional cell carcinomas of the bladder, using the indirect immunoperoxidase technique, β -HCG production was found in 12 of them, 11 of which were grades 3 and 4 transitional cell tumours (Civantos and Rywlin, 1972).

We present 3 patients with advanced transitional cell carcinoma of the bladder who were found to have elevated levels of tumour markers— β -HCG in all cases, and CEA (carcinoembryonic antigen) and AFP (alpha-fetoprotein) additionally in 1.

The success of combination chemotherapy in the treatment of anaplastic germ cell tumours and the value of serial tumour marker estimation in assessing response prompted the adoption of such a regime, and the results are presented and discussed.

Case Reports

Case 1. A 47-year-old man presented with frank haematuria. At cystoscopy a transitional cell carcinoma of the bladder was found. Initial staging of the tumour was not available because he was treated with regular cystodiathermy. Seventeen months later he complained of abdominal discomfort and had developed ascites. At laparotomy there was widespread intra-abdominal tumour, with no apparent primary source. Biopsy of the omentum showed a poorly differentiated mucus-secreting adenocarcinoma of unknown origin. Further investigation revealed axillary lymphadenopathy, bilateral gynaecomastia and ascites. The testes were normal.

After preliminary investigations the serum β -HCG was found to be raised at 2709 iu/l, CEA raised to 23 μ g/l and AFP to 59 ku/l.

Lumbar puncture showed the CSF to have no malignant cells with a β -HCG level of 20 iu/l and AFP <2 ku/l. Ultrasound scan showed a nodule <1 cm in the right lobe of the liver and a 4-cm mass superior and posterior to the bladder. CT scanning of the thorax and abdomen confirmed the presence of ascites and a right pleural effusion.

The original histological specimens from the bladder were compared with the omental biopsy. The bladder specimen showed fibromuscular fragments infiltrated by a carcinoma composed of eosinophilic pleomorphic cells forming clusters and occasional acinar structures. There were frequent mononuclear tumour giant cells and occasional multinucleated tumour giant cells. Acidophilic hyaline inclusions were present in some cells together with necrosis, focal calcification and diathermy artefact.

The omental tumour showed fibrovascular tissue with tumour similar to that in the first specimen, in which glandular formation was more evident. The appearance of both was of a poorly differentiated invasive transitional cell carcinoma, probably of bladder origin, with metastases in the peritoneum.

Because the elevated levels of β -HCG and AFP suggested that the disseminated tumour had features of germ cell differentiation, the patient was treated with combination chemotherapy appropriate to testicular non-seminomatous germ cell tumours.

In view of his poor state at the start of treatment, the initial treatment was low dose cisplatin 20 mg/m² i.v. and etoposide 100 mg/m² i.v.

This was followed by courses of full dose cisplatin (100 mg/m²) with pre-hydration and etoposide 200 mg/m² in 250 ml saline over 30 min alternating with OMB:

Day 1: vincristine 1 mg/m² i.v., methotrexate 300 mg/m² as a 12-h infusion.

Day 2: bleomycin 15 mg by 24-h infusion; folinic acid rescue started at 24 h (after start of methotrexate) in a dose of 15 mg 12-hourly for 4 doses.

Day 3: bleomycin 15 mg by 24-h infusion.

These courses were alternated at 10-day intervals. After 3 courses the axillary nodes were not palpable, ascites

disappeared and β -HCG, CEA and AFP levels dropped rapidly, reaching normal after 8 weeks of chemotherapy (Fig. 1). The chemotherapy was complicated by vomiting and alopecia.

Serial ultrasound scans showed resolution of the bladder mass and CT scanning confirmed the disappearance of the ascites and pleural effusion. Sixteen weeks after starting chemotherapy, cystoscopy showed no trace of intravesical tumour. Chemotherapy was completed at 25 weeks and the patient has been followed up at regular intervals. The germ cell tumour markers have continued to remain within normal limits and there is no sign of clinical recurrence, with further cystoscopies remaining normal.

Case 2. Seventeen years ago a 57-year-old man with haematuria was found to have multiple superficial bladder tumours. He was treated with open cystodiathermy and subsequently with intravesical ethoglucid. He relapsed after 4 years with multiple tumours in the bladder and prostatic urethra and underwent total cystourethrectomy.

He was followed up for a further 13 years, remaining free of recurrent disease, until he presented with vague abdominal pain and was found to have a mass in the right iliac fossa 5 × 100 mm and pulmonary metastases which had not been present 3 years earlier. There was no evidence of gynaecomastia and the testes were normal. Apart from some anaemia, the other abnormal investigation was a serum β -HCG of 161 u/l.

CT scan confirmed the previous findings and revealed no other abnormality apart from the mass in the RIF and involved external iliac nodes. Needle biopsy showed a very poorly differentiated carcinoma replacing lymph nodes. There was marked pleomorphism with bizarre giant multinucleate cells. The cytoplasm was eosinophilic

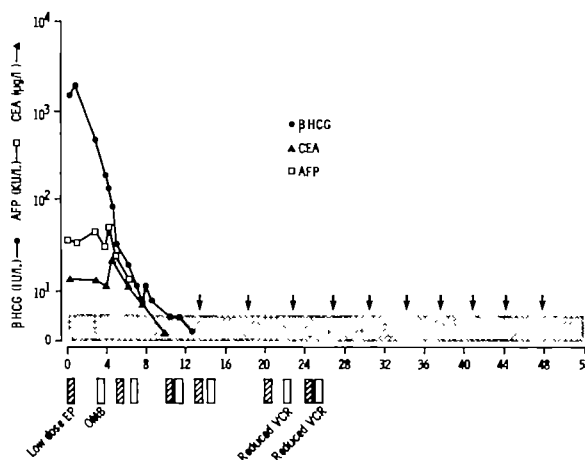


Fig. 1 Case 1. Patient with intra-abdominal metastatic bladder carcinoma. Response to combination chemotherapy is shown by a fall in all tumour markers to normal levels.

EP = etoposide and cisplatin.

OMB = vincristine, methotrexate and bleomycin.

in most areas and one area showed a more trabeculated pattern with clear or vacuolated cytoplasm. The appearances were compatible with recurrence of a transitional cell carcinoma.

In view of the finding of metastatic transitional cell carcinoma with elevated germ cell marker, treatment was started with full dose etoposide and cisplatin alternating with OMB. Courses were alternated at 10-day intervals but the doses of cisplatin and methotrexate were reduced because of mild renal impairment (serum creatinine 250 $\mu\text{mol/l}$). After 4 weeks an improvement was seen in the chest X-ray, although the abdominal mass remained palpable. At 7 weeks the $\beta\text{-HCG}$ level had returned to normal and remained so (Fig. 2).

A total of 8 courses of chemotherapy were given over 11 weeks and following this a CT scan of the abdomen showed the soft tissue mass to be much smaller with a maximum diameter of 5 cm. Associated thickening of the anterior abdominal wall had diminished.

The patient remained well, apart from a resolving peripheral neuropathy 4 months after treatment, but later died.

Case 3. A 54-year-old man presented with a T4 transitional cell carcinoma of the bladder, invading the rectum. He was irradiated to 6600 cGy. Cystoscopy 7 months later showed oedematous areas at the bladder base, although biopsy showed no evidence of recurrent tumour. Bimanual examination showed diffuse thickening of the pelvic tissues consistent with post-radiotherapy changes. He subsequently developed rectal pain, tenesmus and partial left ureteric obstruction. CT scan showed no obvious pelvic or abdominal extension of the tumour,

although there was infiltration of the tissues between the rectum and bladder. Sigmoidoscopy showed rectal involvement and a biopsy confirmed a poorly differentiated transitional cell carcinoma. This was inoperable and a palliative colostomy was carried out. There was no evidence of disseminated disease but $\beta\text{-HCG}$ was elevated to 122 iu/l.

Combination chemotherapy was started, using reduced doses of cisplatin and methotrexate in view of some renal impairment. Treatment was started on a similar chemotherapy protocol as the earlier patients. This resulted in a general improvement in well-being with a reduction in analgesic requirements and a rapid fall in the tumour marker levels (Fig. 3). There was a 6-week interval in the treatment regime when his $\beta\text{-HCG}$ rose steeply, falling again after reinstatement of chemotherapy.

Discussion

The basic biology of human chorionic gonadotrophin and its β subunit is well known. High levels of $\beta\text{-HCG}$ have been found in the sera of patients with tumours of the breast, lung, stomach and testis, in addition to the more frequently described placental and extragonadal choriocarcinoma.

Javadpour (1979) analysed 400 patients with active non-seminomatous germ cell tumours of the testis and found 60% to have elevated serum HCG levels, and 7% of patients with testicular seminomas to have raised levels.

It is now established that secretion of one or

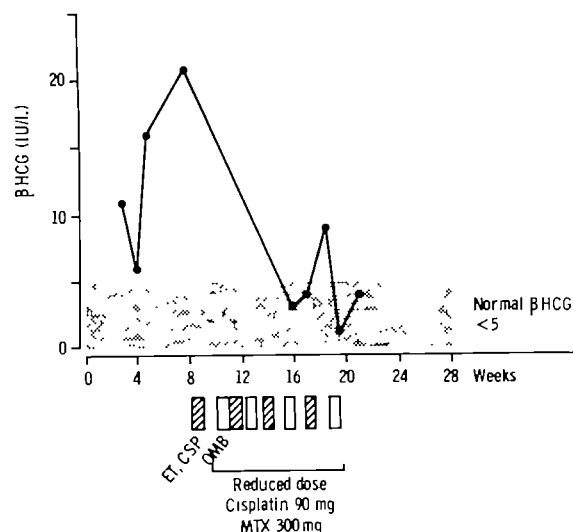


Fig. 2 Case 2. Patient with an abdominal mass and pulmonary metastases, 9 years after total cystectomy, and elevated serum $\beta\text{-HCG}$ levels. Response to chemotherapy.

ET = etoposide.

CSP = cisplatin.

OMB = vincristine, methotrexate and bleomycin.

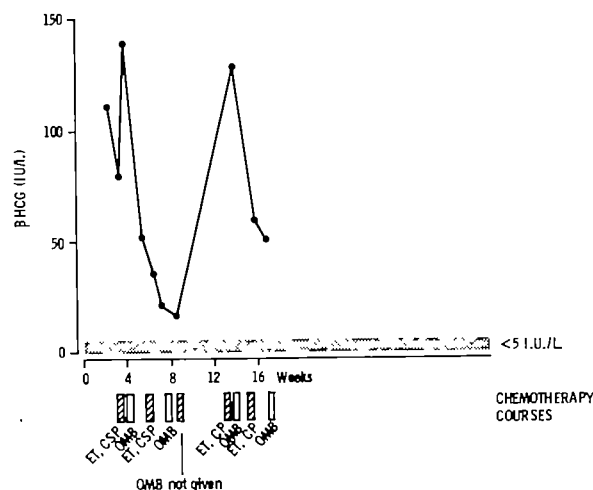


Fig. 3 Case 3. Patient with advanced pelvic recurrence of carcinoma of the bladder following radiotherapy and elevated serum $\beta\text{-HCG}$ levels. The initial response was followed by a relapse which responded promptly to a further course of chemotherapy.

ET = etoposide.

CP/CSP = cisplatin.

OMB = vincristine, methotrexate and bleomycin.

more tumour markers, β -HCG, AFP, placental alkaline phosphatase (PLAP) and lactate dehydrogenase (LDH), occurs in the majority of anaplastic germ cell tumours, and high initial serum concentrations carry adverse prognostic implications. Response to treatment by gonadotrophin-secreting tumours may be measured by a fall in the levels of β -HCG and other markers, and recurrent disease is invariably found if the levels rise subsequently. Although the transitional epithelium of the bladder may show many types of metaplasia, endocrine manifestations are rarely seen, possibly because they are not routinely assayed. Bladder tumours associated with ectopic gonadotrophin production may be either true choriocarcinomas arising in the bladder, or transitional cell carcinomas with the capacity to secrete gonadotrophin. Shah *et al.* (1986) reported that only 11 cases of choriocarcinoma of the bladder had been recorded in the literature since 1904 and only 2 of them were associated with transitional cell carcinoma alone—the remainder being choriocarcinomas alone, elements of choriocarcinoma with transitional cell carcinoma or undifferentiated carcinomas.

Retrospective analysis of 104 cases of transitional cell carcinoma of the bladder by Shah *et al.* (1986), using an indirect immunoperoxidase method for β -HCG, showed 12 to be positive for β -HCG production. In one such biopsy occasional multinucleate giant cells were present and these stained intensely for β -HCG. It is significant that in this case, the serum β -HCG was raised to 25,000 iu/l and after partial cystectomy the level dropped to 3 iu/l. Recorded cases of transitional cell carcinoma associated with β -HCG secretion are rare. The first documented case was of a 74-year-old man who underwent partial cystectomy for a poorly differentiated transitional cell carcinoma, stage T1. The presence of syncytial giant cells in the tumour prompted a search for gonadotrophin production and a titre of 10,000 iu in a 24-h urine specimen was found. This decreased to undetectable levels by the ninth post-operative day.

Five months after operation the patient remained free of recurrence of tumour (Civantos and Rywlin, 1972). Rodenburg *et al.* (1985) reported a further case of poorly differentiated transitional cell bladder carcinoma with bony metastases. No gynaecomastia was evident, but the serum β -HCG was raised at 46 iu/l. No giant cells were seen in the biopsy. In this case chemotherapy according to a germ cell tumour protocol was given; it consisted of cisplatin, vinblastine and bleomycin, but after one course bone pain increased and the β -HCG increased to

90 iu/l with a fatal outcome despite a modified protocol.

The 3 patients in this study represent an attempt to apply a rational scheme of chemotherapy based on the finding of elevated serum germ cell tumour markers. Each presented with advanced disease, either locally invasive or metastatic, and the finding of elevated serum markers suggested the adoption of chemotherapy specifically directed against germ cell tumours.

Newlands *et al.* (1986) used combination chemotherapy in patients with anaplastic germ cell tumours, achieving an overall survival rate of 89%. Of 149 patients with metastatic disease, 134 had a testicular primary, but there were other sites of primary disease: retroperitoneum (7), mediastinum (5), unknown primary site (3).

The response rate was obtained using treatment with POMB/ACE (platinum, vincristine (oncovin), methotrexate, bleomycin, actinomycin D, cyclophosphamide and etoposide). Poor prognostic factors included large tumour bulk and serum concentrations of HCG > 50,000 iu/l and AFP > 500 ku/l. In none of our 3 patients did the serum concentration of β -HCG approach such high levels. Treatment was initiated using a combination of etoposide and cisplatin (EP) and was followed by alternating courses of vincristine, methotrexate and bleomycin (OMB) at 10-day intervals.

Response to treatment was defined as the disappearance of clinical and biochemical evidence of disease. It is of interest that the patient with the highest levels of β -HCG and AFP had a durable complete response, whereas the 2 with more modest production had a partial response.

In case 1 the elevated serum markers returned to normal by 10 weeks, following 2 courses of EP and OMB; these normal levels were accompanied by objective improvement in the clinical evidence of disease. No recurrent disease had occurred.

In case 2, a lower initial level of serum β -HCG was seen to fall with initiation of combination chemotherapy and again objective evidence of tumour resolution was found with CT scans, showing a reduction in volume of the abdominal mass and resolution of pulmonary metastases.

Case 3 illustrates the effect of chemotherapy on locally invasive disease, in terms of reduction of pain intensity and analgesic requirement, again accompanied by a fall in elevated tumour marker levels, and the necessity of continuing surveillance to detect relapse (Fig. 3).

It appears that β -HCG production tends to occur in less differentiated tumours, being associated with

fetal gene expression during oncogenesis associated with the production of other substances such as alphafetoprotein and carcinoembryonic antigen. It may be that production of these markers by transitional cell carcinoma is more common than previously recognised. Since they provide a convenient and easily detectable index of tumour response, as well as an indication that the tumour may be sensitive to an appropriate chemotherapeutic regime directed against anaplastic germ cell elements, then a search for such markers in serum and urine may be of help in planning appropriate treatment.

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Effect of Urine pH on the Stability of Doxorubicin and its Recovery from Bladder Instillations

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Summary—Doxorubicin (1 mg/ml) was shown to be stable when added to urine samples with a mean natural pH of 5.4 and in urine buffered to a mean pH of 4.6. However, at alkaline pH (mean = 8.1) there was a biphasic degradation of doxorubicin (mean $t_{1/2}$ = 3.24 and 89 h respectively). The data indicate that buffering intravesical doxorubicin to pH 4.6 (acetate buffer) or pre-dosing of patients with ammonium chloride may minimise loss of active drug during the time for which the drug is retained in the bladder. Recovery of doxorubicin following 1 hour's retention in the bladder was similar (77%) for doses of 38/48 or 78 mg. It is suggested that a dose of 50 mg (1 mg/ml) is sufficient to ensure an adequate delivery of active drug to the bladder wall.

Doxorubicin is an anthracycline antitumour antibiotic which intercalates with DNA and inhibits both DNA and RNA synthesis (Riggs and Bachur, 1983). Repeated intravesical therapy with doxorubicin has been successful in decreasing or preventing the recurrence of superficial transitional cell carcinomas of the bladder (Pavone-Macaluso, 1971; Ozaki, 1977; Edsmyr *et al.*, 1980; Garnick *et al.*, 1984). Following such administration, the drug is accumulated by both normal bladder epithelium and tumour tissue (Garofalo *et al.*, 1985; Nakada *et al.*, 1985) but there is negligible systemic absorption (Jakobi and Kurth, 1980; Lundbeck *et al.*, 1981; Garofalo *et al.*, 1985) and 84 to 100% of the dose can be recovered by drainage of the bladder (Lundbeck *et al.*, 1981). These observations suggest that the dose regimens of 80 to 100 mg per treatment recommended by some authors (Lundbeck *et al.*, 1981; Garnick *et al.*, 1984; Adriamycin[®] Product Information) may be much higher than is necessary. Indeed, several studies have shown that a dose of 50 mg per instillation is highly effective (Blinst Italian Cooperative Group, 1984; Kurth *et al.*, 1984; Nakada *et al.*, 1985; Khanna *et al.*, 1988).

Our interest in doxorubicin was stimulated by

the high cost of the usual recommended 12-month treatment course which varies from A\$ 2 to 3000 depending on the dose chosen. Initially, we instituted a study designed to evaluate whether sufficient unchanged doxorubicin could be recovered from instillates to warrant a commercial operation to repurify the active drug for subsequent re-use. However, urinary recoveries were highly variable (20–88%). Since systemic absorption of intravesical doxorubicin is minimal (Jakobi and Kurth, 1980), we reasoned that the variable recovery might be due to a time-related degradation of the drug. The present study was designed to investigate the latter possibility. Our data indicate that urine pH has a marked influence on the stability of intravesical doxorubicin.

Patients and Methods

Drugs

Doxorubicin hydrochloride (Adriamycin[®]) was obtained from Farmitalia Carlo Erba Pty Ltd, Australia. Daunorubicin (Cerubidin[®]) was obtained from May and Baker, Australia.

Preparation of bladder instillations

The bladder instillations were prepared by recon-

stituting vials containing 50 mg of lyophilised doxorubicin hydrochloride in 50 ml of Water for Injections BP: Sodium Chloride Injection BP (1:1). The appropriate dose was packed in 50 ml luer-lock syringes (Terumo Corporation, Japan). A 2-ml aliquot of each solution was reserved for quality assurance analysis. Solutions were not refrigerated and were instilled within 4 h of preparation. Preliminary studies indicated that these instillations were stable for at least 48 h after preparation.

Patients

Nine patients (7 men and 2 women) with an average age of 71 years (range 47–88) were entered into the study. All had a history of 4 or more endoscopic resections or of cysto-diathermy of recurrent superficial transitional cell bladder carcinomas within the preceding 12 months. Biopsies from all 9 patients showed that their lesions were Ta or T1. On arrival in the clinic, patients were asked to empty their bladders; they were then catheterised and a solution of doxorubicin was instilled (38, 48 or 78 mg). The catheter was immediately withdrawn and the patient instructed to lie on alternate sides for 2×30 min and the contents of the bladder were then voided. Treatments were repeated at monthly intervals for 12 months.

Urine collections

At the end of the 1-h treatment period, a total urine collection was made (by voiding) and the volume of the sample recorded. A 20-ml aliquot of each sample was mixed immediately with 5 ml of 0.5 M acetate buffer (pH 4.0), refrigerated at 4°C and transported to the laboratory within 72 h for analysis of doxorubicin content.

Measurement of doxorubicin in urine

High performance liquid chromatographic (HPLC) analysis was carried out by the method of Minchin and Boyd (1983) with minor modifications. Buffered urine or doxorubicin standards (0.1 ml) were diluted to 10 ml with a 20 µg/ml solution of daunorubicin (internal standard) in 0.9% sodium chloride solution. Aliquots (30 µl) were then injected on to the HPLC system which consisted of a Waters Associates µ-Bondapak C₁₈ column with a mobile phase of 30% acetonitrile in 50 mM sodium formate buffer (pH4), pumped at a flow rate of 2.5 ml/min. Eluting peaks were detected by their ultra-violet absorbance at 234 nm. Under these conditions, approximate retention times for doxorubicin and daunorubicin were 4 and 6 min respectively. A standard curve was analysed with each batch of samples and was

shown to be linear over the range 0.05 to 1.2 mg/ml with a within-day coefficient of variation of 7.7 and 2.4% (n = 5) at 0.1 and 1.0 mg/l respectively.

In vitro stability of doxorubicin in urine

Doxorubicin, at a final concentration of 1 mg/ml, was added to control urine samples with a natural pH >7 (n = 5) or <7 (n = 5). In addition, 5 aliquots of urine with a pH >7 (20 ml) were mixed with 5 ml of 0.5 M acetate buffer (pH 4.0) and doxorubicin was then added to a final concentration of 1 mg/ml. The concentration of doxorubicin was then assayed immediately after addition of the drug and 1, 2, 5 and 7 days later.

In a separate study, doxorubicin (1 mg/ml final concentration) was added to 4 control urine samples with a pH of 8.15 ± 0.15 and drug content was assayed by HPLC at 0, 2, 4, 6, 24, 48, 120 and 168 h.

Analysis of data

Data are summarised as mean $\pm$ s.e.m. Data for the stability of doxorubicin in urine at various pH values were analysed by analysis of variance and differences between means were identified using Fisher's least significant differences (LSD) test. For the detailed analysis of doxorubicin degradation in alkaline urine, urinary concentration data were fitted to a biexponential equation by non-linear least squares regression analysis (Knott, 1979). Pseudo first order rate constants of degradation (the exponents of the equation) were estimated for 4 different samples and data summarised as mean and range. Mean recovery data at different dose levels were compared with Student's *t* test.

Results

The effect of pH on the concentration of doxorubicin added to control urine samples is shown in Figure 1. Analysis variance indicated that there were significant differences ($P < 0.001$) between the 3 pH groups studied and between study days. At natural pH values >7 (8.11 ± 0.12) there was a marked time-related decrease in concentration to around 15% after 7 days which was shown to be significant using Fisher's LSD test. For urine samples with a natural pH <7 (5.41 ± 0.24) there was little evidence for decomposition, except on day 7. Doxorubicin appeared to be stable (not significantly different by Fisher's LSD test) in urine samples where the pH was adjusted to a final value of 4.6 ± 0.13 by the addition of acetate buffer. The detailed time course of doxorubicin decomposition in alkaline urine is shown in Figure 2. There was

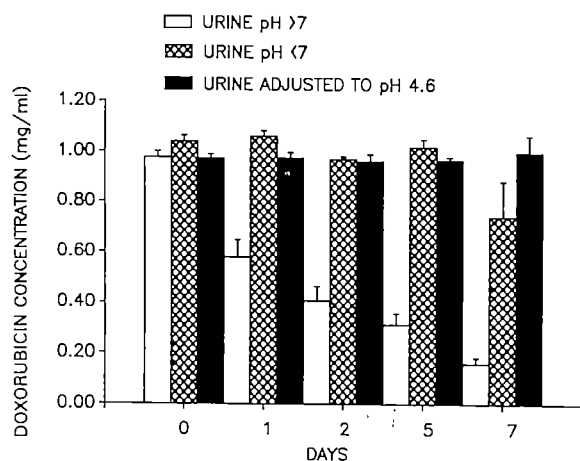


Fig. 1 Effect of time of storage on doxorubicin concentration in urine samples with natural pH values >7 (mean = 8.11, $n=5$), <7 (mean 5.41, $n=5$) or adjusted to pH 4.6 with acetate buffer ($n=5$).

an initial rapid rate of degradation with a mean pseudo first order rate constant of 0.214/h (range 0.087–0.31) and a second much slower first order decay with a mean rate constant of 0.008/h (range 0.006–0.009). There was no evidence of any extra ultra-violet absorbing peaks in the chromatographic analysis of these samples.

Recovery of doxorubicin from bladder instillations given to 9 patients on 27 different occasions is summarised in the Table: Overall recovery was $76.7 \pm 2.8\%$ (range 42.1–95.9). In 2 patients, collection of urine for an additional 1 h after the end of the treatment only resulted in an extra 2.2% of the additional dose being recovered. Recovery of doxorubicin for the combined 38 and 48 mg doses ($77.5 \pm 6.6\%$; $n=7$) was not significantly different

Table Recovery of Doxorubicin from Bladder Instillations

Patient	Dose (mg)	No. of studies	Percent recovered (mean)
1	48	3	68.6
	78	3	91.6
2	38	2	94.7
	78	3	69.2
3	78	5	86.5
4	48	1	70.8
5	48	1	76.6
6	78	1	42.1
7	78	4	67.7
8	78	3	78.6
9	78	1	65.8

($P=0.87$) from that for the 78 mg dose ($76.5 \pm 3.1\%$; $n=20$).

Discussion

Decomposition of doxorubicin in solutions/buffers of various pH values has previously been reported (Poochikian *et al.*, 1981; Wasserman and Bungard, 1983; Janssen *et al.*, 1985). Only one of these studies has examined the decomposition above pH 7 (Janssen *et al.*, 1985) and, although they did not identify the initial rapid degradation phase ($t_{1/2}=3.24$ h) seen in our study, their reported first order rate constants were similar to that for the second slower phase ($t_{1/2}=89$ h) seen with our data. However, careful examination of their plots of log percent doxorubicin remaining versus time in phosphate buffer (pH 7.4) shows that the zero time intercepts are 90 to 95% of the initial concentration of doxorubicin (50 $\mu\text{g/ml}$). These data are consistent with the presence of an initial rapid degradation phase as found in our experiments. Maximum stability was reported in Glucose 5% Injection at a pH value of 4.5 (Poochikian *et al.*, 1981), which is consistent with the excellent stability observed at pH 4.6 in the present study. The biphasic nature of the degradation suggests that 2 different chemical pathways may be involved in the degradation of the drug in alkaline urine. While the degradation products of doxorubicin at alkaline pH have not been identified, Janssen *et al.* (1985) did report the presence of 2 unidentified peaks in their HPLC analyses. Neither of these was doxorubicinone.

There are 2 important consequences which follow from the identification of the initial rapid degrada-

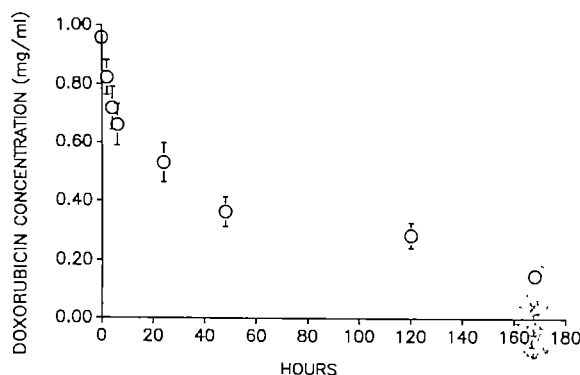


Fig. 2 Degradation of doxorubicin (1 mg/ml) in urine with a mean pH value of 8.15. Results as mean $\pm$ s.e.m. ($n=5$).

tion phase for doxorubicin. Firstly, when doxorubicin is to be quantified in urine (especially if urinary pH is > 7), samples need to be adjusted to a pH of approximately 4.5 immediately after collection. Secondly, for those patients who produce an alkaline urine, there may be substantial degradation of doxorubicin during the time for which the instillation is left in the bladder (usually 1–2 h). This loss of active drug with possible associated loss of therapeutic efficacy could be minimised either by preparing the doxorubicin bladder instillations in a suitable buffer or by acidifying the patient's urine by pre-dosing with oral ammonium chloride. However, the decrease in active drug concentration which may result in an alkaline urine needs to be considered in conjunction with recent findings on the *in vitro* cytotoxicity of doxorubicin at different pH values (Groos *et al.*, 1986). Using RT112 cells in culture, these authors were able to show an approximate 50% increase in cytotoxicity of doxorubicin when the pH of the culture medium was increased from 5 to 8. An increase in the proportion of non-ionised doxorubicin with consequent increase in cellular uptake by passive diffusion was suggested as the mechanism for their observation.

Recovery of both the 38/48 and 78 mg doses of doxorubicin was similar at 77%. Thus some 23% of the instilled dose was either retained in the bladder, presumably bound to the bladder wall (Jakobi and Kurth, 1980; Nakagawa *et al.*, 1987), or was degraded during the treatment period. Since we were not able to measure urine pH in these patients, we cannot dissect out the individual contributions of these 2 possible mechanisms of doxorubicin loss. From our *in vitro* studies, it seems likely that degradation would be significant only in those patients producing an alkaline urine (approximately 20% of patients in a random test of 50 fresh urine samples) and could account for some 12% of the initial dose during 1 hour's treatment. Thus it would seem that both of the doses studied would deliver a considerable excess of active drug to the bladder wall. In the interests of health care costs, the lower (50 mg) dose, which is well documented to be highly effective in the treatment of both completely and incompletely resected tumours (Blinst Italian Cooperative Group, 1984; Kurth *et al.*, 1984; Nakada *et al.*, 1985; Khanna *et al.*, 1988) is therefore to be preferred.

The fact that some 77% of the initial doxorubicin dose is still present in acetate stabilised instillates from patients suggests that this unchanged drug could conceivably be recovered by a technique such

as preparative scale HPLC. Recrystallisation and proof of conformance with an appropriate pharmacopoeial standard would then be necessary. The commercial viability of such an operation would require either that the process be sited in a large centre where many doxorubicin instillations were routinely undertaken or that instillations were able to be obtained from several smaller centres.

Acknowledgements

We thank Fremantle Hospital for generous funding and Messrs A. Tulloch and D. Chelvanayagam for permission to include 2 of their patients in the study.

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Urine Flow Rates in Male and Female Urodynamic Patients Compared with the Liverpool Nomograms

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Summary—The Liverpool male and female nomograms provide normal reference ranges for the maximum and average urine flow rates over a wide range of voided volumes. A known urine flow rate, in combination with the respective voided volume (and in men the age), can be converted into an equivalent centile ranking, using the equation for the relevant nomogram. Centile rankings allow the urine flow rates of specific male and female populations to be compared.

The maximum and average urine flow rates of urodynamic patients (504 consecutive male and 168 consecutive female) were converted into centile rankings. These centile rankings were then compared with the respective urodynamic diagnoses.

The median centile rankings for their maximum and average urine flow rates were 21 and 11 (male) respectively and 31 and 18 (female) (vs 50 for the normal populations). The low urine flow rates applied to all diagnostic groups, including those symptomatic men and women who were found to be urodynamically normal. Low urine flow rates may be one of a number of subtle manifestations of urological disease in these patients.

Men with obstruction and women with voiding difficulties had the lowest urine flow rates. The 25th centile (men) and the 10th centile (women) appeared to be most appropriate lower limits of normality for both urine flow rates to identify those men more likely to be obstructed and those women at higher risk of voiding difficulties.

Men and women with detrusor instability had the highest urine flow rates. Detrusor instability was present in 71% of men with centile rankings for the maximum urine flow rate over 50; 50% of women whose maximum urine flow rate centiles were over 90 had detrusor instability.

The Liverpool male and female nomograms, based on studies of 331 asymptomatic men and 249 asymptomatic women under specific conditions of environment and equipment, were constructed by Haylen *et al.* (1989) to provide normal reference ranges for the maximum and average urine flow rates over a wide range of voided volumes. The equations used for these nomograms incorporate the strong dependence of urine flow rates in normal men and women on voided volume.

A known flow rate in combination with the respective voided volume (and in men the age), can be converted using the relevant nomogram equation into a centile ranking, *i.e.* the centile line on the

nomogram on to which these data will fall. These centile rankings were shown by Haylen *et al.* (1989) to be consistent in successive voids. By the use of centile rankings, urine flow rates in different male and female populations can be compared.

Uroflowmetry has long been recommended as a screening test for obstruction in men (Abrams and Griffiths, 1978; Drach *et al.*, 1979) and voiding difficulties in women (Peter and Drake, 1958; Axelrod and Blaivas, 1987). Little, however, is known of how the other forms of lower urinary tract dysfunction affect urine flow rates in either sex.

This study compares the urine flow rates of men and women attending for urodynamic investigations (urodynamic patients) in all diagnostic cate-

gories, by the use of centile rankings, with those of the normal populations used in the construction of the Liverpool male and female nomograms. It then seeks to assess the value of urine flow rate measurement (uroflowmetry) in individual urodynamic diagnoses.

Patients and Methods

Urodynamic patients (504 consecutive men aged 14 to 94 years, and 168 consecutive women aged 18 to 84) referred for urodynamic studies because of urological symptoms were recruited for the study.

In all cases a full history was taken and a full examination carried out. A midstream sample of urine was examined bacteriologically. All women underwent a 2-h Liverpool pad test (Sutherst *et al.*, 1981). All patients voided in private over a calibrated Urolyn 1000 mictograph (Dantec, Denmark). Low urine flow rates or unusual flow patterns were repeated. The residual urine volume was measured by urethral catheterisation and repeated if over 50 ml.

Urodynamic testing included filling and provocative subtraction cystometry, urethral pressure testing at rest and during stress (women) and synchronous video/pressure/flow urodynamic studies (men). All definitions and units conform with the standards proposed by the International Continence Society (1976, 1977) except where specifically noted.

The urine flow rates (maximum and average) and the respective voided volumes of all patients were then noted. These data were converted into centile rankings, using the equation and variance for the relevant Liverpool nomogram (Haylen *et al.*, 1989). These centile rankings were then classified according to the final urodynamic diagnosis obtained after full urodynamic assessment. Only the raw urine flow rates (and not the respective centile rankings) were known to the clinician in determining the final urodynamic diagnoses. Medians (50th centiles) and interquartile ranges (25th to 75th centiles) are used for presentation of the centile rankings.

The sensitivities and specificities of the maximum and average urine flow rates in predicting bladder outflow obstruction in men (alone or combined with detrusor instability) were assessed (a) at the 10th centile, (b) at the 25th centile, (c) and (d) at the 10th and 25th centiles respectively in combination with the residual urine volume measurement (upper limit of normality taken to be 50 ml). The sensitivity and specificity of the residual urine volume alone were also assessed.

Results

The median centile rankings for the maximum urine flow rate were 21 (interquartile range 5–46: men) and 31 (interquartile range 7–59: women). The median centile rankings for the average urine flow rate were 11 (interquartile range 2–35: men) and 18 (interquartile range 2–53: women).

Tables 1 (male patients) and 2 (female patients) show the median (50th) centile rankings and interquartile ranges (25th–75th centiles) for the maximum and average flow rates separated accord-

Table 1 Median Centile Rankings (and interquartile range) for Maximum (MUFR) and Average (AUFR) Urine Flow Rates in Male Urodynamic Patients Classified According to Diagnosis

<i>Urodynamic diagnosis</i>	<i>No.</i>	<i>MUFR Median centile (25th–75th)</i>	<i>AUFR Median centile (25th–75th)</i>
Detrusor instability (DI) alone	149	41 (19–66)	31 (8–56)
DI plus obstruction	124	15 (5–39)	7 (2–21)
Obstruction alone	161	9 (1–31)	3 (0–19)
Normal (after urodynamics)	70	29 (9–50)	18 (4–38)

Table 2 Median Centile Rankings (and interquartile ranges) for Maximum and Average Urine Flow Rates and Voided Volumes of Female Urodynamic Patients Separated According to Urodynamic Diagnosis. (Data from 20 women with mixed diagnoses (apart from GSI/DI) have not been included)

	<i>No.</i>	<i>MUFR Median centile (25th–75th)</i>	<i>AUFR Median centile (25th–75th)</i>
Genuine stress incontinence (GSI)	65	34 (12–63)	27 (6–66)
GSI + DI	11	21 (14–53)	26 (1–50)
Detrusor instability	35	38 (18–68)	28 (2–70)
Voiding difficulty	6	1 (1–3)	1 (0–1)
Sensory disorder	10	16 (5–69)	19 (1–60)
Normal (after urodynamics)	21	23 (8–36)	14 (6–36)

ing to the respective urodynamic diagnoses. For reasons of clarity of presentation in Table 2, the centile rankings of the many permutations of mixed diagnoses (apart from combined genuine stress incontinence (GSI)/detrusor instability (DI)), which account for a further 20 women, are not included.

Tables 3 (male patients) and 4 (female patients) show the number (percentage) of urine flow rate centiles of the male and female urodynamic patients in each diagnostic group lying either above the 90th

centile or below the 10th centile. Of the 20 women with mixed diagnoses other than GSI/DI, 12(60%) include the diagnosis of voiding difficulties. These have been included in Table 4 as a separate group.

Table 5 shows the sensitivities and specificities of the maximum and average urine flow rates in diagnosing bladder outflow obstruction (alone or in combination with detrusor instability) in male urodynamic patients depending on whether the lower limit of normal for either the maximum and average urine flow rates was at (a) the 10th centile, (b) the 25th centile, (c) and (d) the 10th and 25th centiles in combination with the residual urine volume measurement (upper limit of normal taken at 50 ml). The sensitivity and specificity of the residual urine volume measurement alone in detecting obstructed men were also assessed (e).

Table 6 shows the median centiles (and interquartile ranges) of the male urodynamic patients diagnosed as obstructed and subclassified according to the site of the obstruction.

Table 3 Numbers (percentage) of Male Urodynamic Patients with Urine Flow Rates either under 10th Centile or over 90th Centile, Classified According to Urodynamic Diagnosis

Urodynamic diagnosis	No.	Under 10th centile		Over 90th centile	
		MUFR	AUFR	MUFR	AUFR
Detrusor instability (DI) alone	149	27 (18%)	39 (26%)	11 (7%)	6 (4%)
DI plus obstruction	124	46 (37%)	69 (56%)	3 (2%)	2 (1%)
Obstruction alone	161	86 (53%)	108 (67%)	0 (0%)	0 (0%)
Normal (after urodynamics)	70	18 (26%)	25 (36%)	2 (3%)	2 (3%)

Discussion

The median centile rankings for both the maximum and average urine flow rates of the male and female urodynamic patients were much lower than those of the respective normal populations (median centile 50 by definition). The lower urine flow rate centiles applied to all diagnostic groupings, includ-

Table 4 Numbers (percentage) of Urine Flow Rates in each Diagnostic Group either below 10th Centile or above 90th Centile. (Data from the 8 women with mixed diagnoses (apart from GSI/DI or those which include voiding difficulty) have not been included)

Urodynamic diagnosis	No.	Under 10th centile (%)		Over 90th centile (%)	
		MUFR	AUFR	MUFR	AUFR
Genuine stress incontinence (GSI)	65	14 (22%)	22 (37%)	3 (5%)	2 (3%)
GSI + DI	11	2 (18%)	4 (40%)	0 (0%)	0 (0%)
Detrusor instability	35	7 (20%)	10 (29%)	6 (17%)	3 (9%)
Voiding difficulty	6	6 (100%)	6 (100%)	0 (0%)	0 (0%)
Mixed diagnoses including voiding difficulty	12	8 (67%)	11 (92%)	0 (0%)	0 (0%)
Sensory disorder	10	5 (50%)	4 (40%)	1 (10%)	1 (10%)
Normal (after urodynamics)	22	7 (32%)	9 (43%)	2 (9%)	0 (0%)

Table 5 Sensitivities and Specificities of Maximum and Average Urine Flow Rates in Diagnosing Bladder Outflow Obstruction in Male Urodynamic Patients with Lower Limit of Normal at (a) 10th Centile, (b) 25th Centile, (c) and (d) 10th and 25th Centiles, in Combination with an Upper Limit of Normal for Residual Urine Volume (RUV) at 50 ml

	Centiles	Sensitivity (%)	Specificity (%)
Maximum urine flow rate	10th	46	79
	25th	69	65
	10th and/or RUV > 50 ml	74	65
	25th and/or RUV > 50 ml	86	54
Average urine flow rate	10th	62	70
	25th	81	51
	10th and/or RUV > 50 ml	81	59
	25th and/or RUV > 50 ml	91	43
Residual urine volume (alone)		54	82

Table 6 Median Urinary Flow Rate Centiles (and interquartile ranges) of Male Urodynamic Patients Classified as Obstructed and Subclassified According to Site of Obstruction

Diagnosis	No.	Maximum urine flow rate median centile (25th–75th)	Average urine flow rate median centile (25th–75th)
All obstruction	161	9 (1–31)	3 (0–19)
Bladder neck obstruction	66	3 (0–18)	2 (0–14)
Prostatic obstruction	75	12 (2–35)	5 (0–25)
Sphincteric obstruction	18	10 (1–36)	2 (0–17)

ing those symptomatic men and women who were categorised as “normal” after no urodynamic abnormality was found. Low urine flow rates may be one of a number of more subtle manifestations of urological dysfunction in these patients. These findings also support the normality of the asymptomatic men and women who took part in the Liverpool nomogram study (Haylen *et al.*, 1989).

The lowest urine flow rates were found in men with obstruction and women with voiding difficulties as sole diagnoses (median centile rankings for the maximum urine flow rate 9 and 1 respectively). In women, the 10th centile for both urine flow rates,

especially for the average urine flow rate, appeared to be a useful lower limit of normality to discriminate between those women unlikely to have voiding difficulties (centiles over 10) and those women at higher risk of voiding difficulties (centiles under 10). In women in this group after repeated testing, pressure/flow studies should be considered, looking for the cause of the low urine flow rate.

In men, obstruction was the largest urodynamic diagnosis. The ability of screening tests such as the urine flow rate and the residual urine volume measurements to detect obstructed men correctly is best judged by the sensitivity. From Table 5, the 25th centile would appear to be an appropriate lower limit of normality for both the maximum and average urine flow rates in male urodynamic patients. The sensitivities of the maximum and average urine flow rates in correctly detecting men with obstruction at this level were 69 and 81% using a low urine flow rate alone, or 86 and 91% respectively using a low urine flow rate in combination with a high residual urine volume.

Achieving such high sensitivity levels for the urine flow rate measurement in correctly detecting obstructed men meant here a relatively low rate of correct elimination of non-obstructed men (specificity). Abnormally low urine flow rates in men generally implies the need for more complex voiding studies, including voiding cystometry and videocystourethrography, in order to confirm the diagnosis of obstruction and identify the site of the obstruction. The results show that most symptomatic men, both obstructed and non-obstructed, will require this more complex testing on the basis of abnormal uroflowmetry results. Using the 25th centile as the lower limit of normal for the maximum and average urine flow rates, 54 and 67% respectively of the patients in this study would have required these more complex studies on the basis of a low urine flow rate alone, or 69 and 76% respectively on the basis of a low urine flow rate and/or a high residual urine volume.

In Table 6, obstruction at the bladder neck is seen to cause a much greater impairment to flow rates than obstruction at either a prostatic or distal sphincteric level. Most patients in this group were found to have detrusor/bladder neck dyssynergia. The uroflowmetry findings may therefore be explained by the proposed mechanism of Bates *et al.* (1975) for this disorder, that the obstructive bladder neck becomes tighter during micturition than at rest. Thus the urine flow rates may reflect a relatively greater degree of obstruction in this dynamic disorder compared with static forms of obstruction.

The value of the higher centiles of the nomograms is seen in their ability to predict the urodynamic diagnosis of detrusor instability. As seen in Table 3, 14 of 16 male urodynamic patients (88%) whose centile rankings for the maximum urine flow were over 90 had detrusor instability (either alone or mixed with obstruction). Further analysis has shown that 71% of maximum urine flow rate centiles of 50 or greater and 86% of 75 or greater were in men with detrusor instability. These data provide statistical support for the observations of Schafer and Abrams (1979) and Mundy (1985) concerning the higher incidence of high flow rates in men with detrusor instability. They also show the inadequacy of previous urinary flow rate nomograms (Siroky *et al.*, 1979; Kadow *et al.*, 1985), which concentrated below the line of the mean, in the belief that it was most important how slowly male urodynamic patients voided and not if they had particularly fast urine flow rates. The pattern of a high incidence of very fast urine flow rates in women with detrusor instability was less pronounced, though the same condition was diagnosed in 50% of those whose centile ranking for the maximum urine flow rate was over 90.

In the largest female urodynamic diagnostic group, genuine stress incontinence, over 20% will have urine flow rates under the 10th centile, putting them at higher risk of voiding difficulties. The group of women having sensory urgency as a final diagnosis had a high incidence of low flow rates (median centile ranking for the maximum urine flow rate 16).

The value of uroflowmetry is seen therefore in all diagnostic categories. In particular, voiding difficulty can be excluded in most women by this test. In most symptomatic men, uroflowmetry will not be sufficient to differentiate between obstructed and non-obstructed men. Uroflowmetry will identify a subgroup of symptomatic men with fast maximum urine flow rates who are likely to have detrusor instability.

Centile rankings based on the Liverpool male and female nomograms allow urine flow rates in different male and female populations to be compared accurately by a statistical technique that allows for the variation in urine flow rates with voided volume.

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The “Clam”: Indications and Complications

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Summary—We have reviewed 78 patients who underwent “clam” enterocystoplasty as part or all of their lower urinary tract reconstruction. Nearly half (32) were non-neuropathic; the remainder were either overtly neuropathic (mainly spina bifida) or suspected neuropathic (mainly the older primary enuretics). Only 5 were non-walkers—all neuropathic. Most patients were operated on for incontinence but 12 had upper tract damage related either to urinary diversion or to poor bladder compliance in the early phase of filling; 69 patients became dry, voiding spontaneously (30), by activation of an artificial urinary sphincter (17) or by self intermittent catheterisation (22). Four patients still have nocturnal enuresis, 3 diurnal enuresis and 2 have stress incontinence. One patient has had a continent diversion. The “clam” procedure has revolutionised bladder reconstruction. Careful review has failed to predict the small number who do not achieve a perfect result.

The introduction of the “clam” enterocystoplasty (Bramble, 1982) has transformed the treatment of both recalcitrant idiopathic and neuropathic detrusor dysfunction (Mundy and Stephenson, 1985; Stephenson and Mundy, 1985), provided that in the latter group the bladder is not so severely fibrotic and sacculated as to be unusable. A modified “clam” is also the procedure of choice in undiversion provided the bladder capacity can be brought up to about 150 ml.

Patients and Methods

A total of 78 patients who had undergone “clam” enterocystoplasty as part or all of their bladder reconstruction were reviewed. Follow-up ranged from 6 months to 6 years, with an increasing number of operations performed each year (Fig. 1). There was a preponderance of younger patients, mostly neuropathic or congenital, but also a large middle-aged group mostly with idiopathic instability (Fig. 2).

Non-neuropathic patients (32)

Most of these patients (27) had recalcitrant phasic detrusor instability. All had received conservative treatment, usually terodiline, oxybutinin and bladder training, and in a small number (5) phenolisation, without success. Only 3 patients with poor compliance (late in filling) were “clammed”, underlining the fact that most of these patients have less severe symptoms and respond to non-operative techniques. Unacceptable urge incontinence was a prerequisite for surgery in this group.

Neuropathic patients (26)

All but 4 had congenital myelodysplasia as the cause of their neuropathy. All 12 with impaired renal function (IRF) were from this group; 9 patients had previously been diverted and 5 of the IRF group were undiverted because of progressive renal damage. Altogether there were 15 patients with poor compliance early in filling, which is known to be a poor prognostic sign (Weston *et al.*, 1989). Seven completed the IRF group; another 7 thought originally to have acontractile bladders (Rickwood *et al.*, 1982) developed poor compliance between 6 months and 5 years after implantation of an artificial urinary sphincter (AUS). All have subsequently been “clammed” to re-establish con-

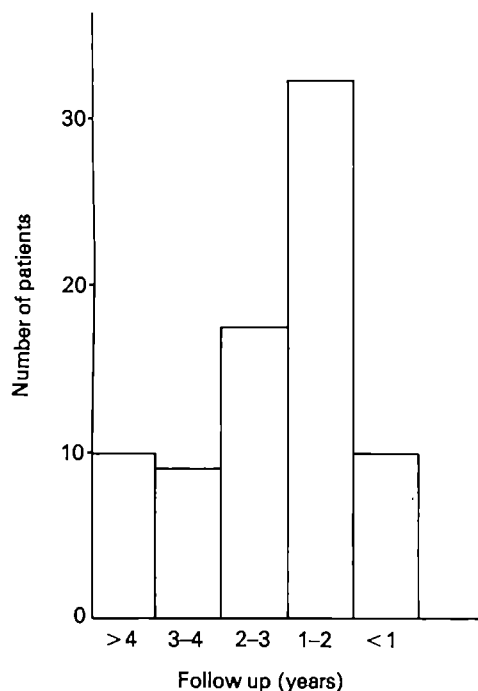


Fig. 1 Number of "clams" per year and period of follow-up.

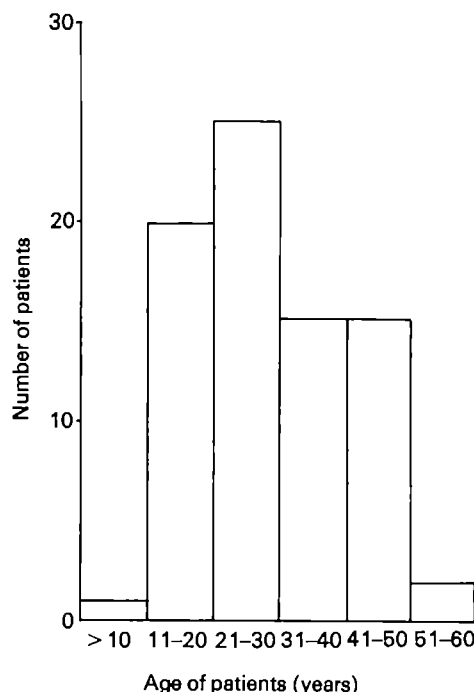


Fig. 2 Age distribution of patients with "clams".

tinence and it is our current practice when implanting an AUS into a patient with an apparently acontractile bladder to "clam" the bladder routinely at the same time.

Of the neuropathic group, most (20) had an AUS implanted at the time of a "clam". A sphincterotomy at 12 o'clock 6 weeks before reconstruction remains standard practice. With undiversion and with some of the girls, sphincterotomy may be neither feasible nor desirable and we tend not to use the AUS, particularly in the young female because of the risk of erosion. The technique with undiversion is usually different, since the bladder rarely cycles to more than 150 to 200 ml, though it is always supple and easy to work with. The bladder is split very anteriorly so that the whole bladder forms the posterior wall of the "clam" (Fig. 3). If the ureters are very dilated, the proximal end of the loop is tapered and a Hendren type reimplant troughed into this posterior wall which is hitched to the psoas. A separate segment of ileum is then used to complete the "clam" and it forms most of the anterior wall of the bladder (Fig. 4). One patient presented shortly after transplantation with a dilating kidney; he was found to have poor compliance early in filling and in this instance the bladder must be split from front to back, but it works just as effectively.

The congenital group (20)

It seems likely that these patients with life-long nocturnal and diurnal enuresis must have a neuropathic element. Certainly in our experience they are very recalcitrant to conservative treatment. The age range in this group was 8 to 31 years, but the average was 17 years, and the child had to be severely incapacitated if less than 15 because of the possibility of spontaneous resolution. The use of night studies is beginning to demonstrate gross instability in about one-third of patients in this group who have normal urodynamics in the laboratory (Fig. 5). It remains to be seen how they respond to treatment.

Results

The non-neuropathic patients

In this group 25 are dry, although 8 have to self-catheterise. Two patients remain wet at night, 1 remains urge incontinent during the day and 2 remain stress incontinent. Two of the 3 artificial urinary sphincters were removed because of infection or erosion; 1 patient remains dry on self intermittent catheterisation (SIC), but the other came (eventually) to a Mitrofanoff procedure. Reassessment of the pre-operative filling and

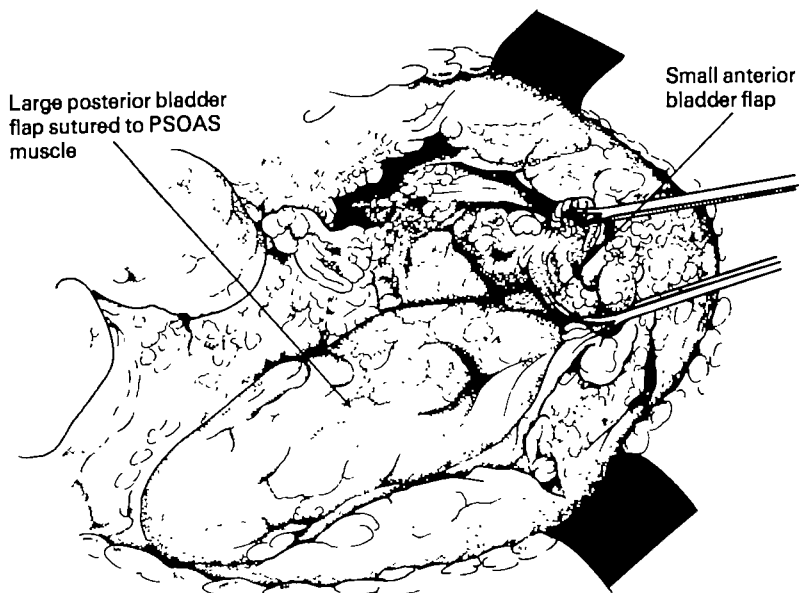


Fig. 3 Technique of "clamming" with a small bladder during undiversion.

voiding patterns did not predict the small number with persistent symptoms or those with voiding difficulty after surgery.

The neuropathic group

This has been a rewarding group; 9 of the 12 patients with hydronephrosis improved and the other 3 stabilised. A high incidence of revisions was required in those with an AUS, but 16 have a

functioning prosthesis, although 6 still have to self-catheterise, as does 1 other patient. The remainder are able to void spontaneously. One patient with an AUS is wet at night when he gets infected, and 1 has stress incontinence.

The congenital group

All but 2 patients are dry, though 8 have to self-catheterise (Fig. 6). Both of those with persistent

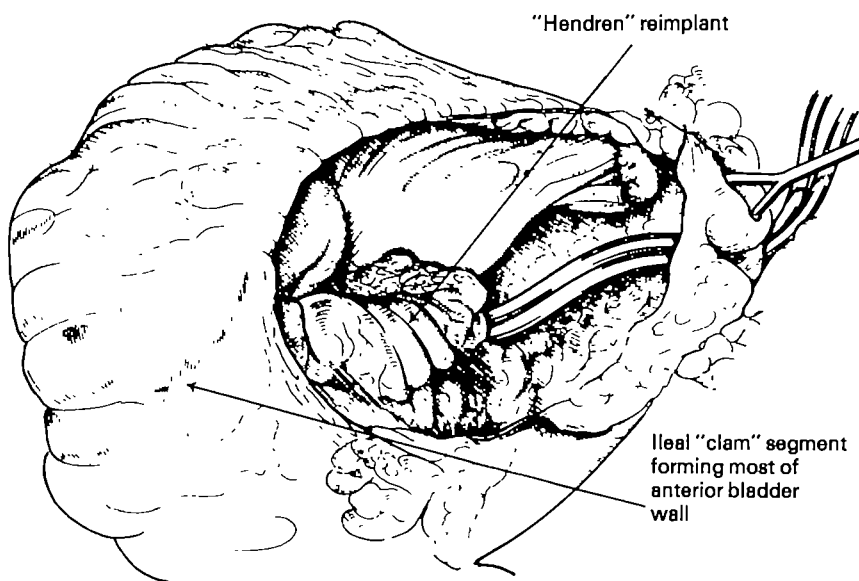
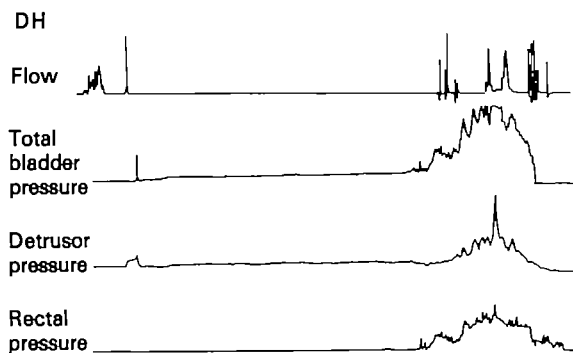
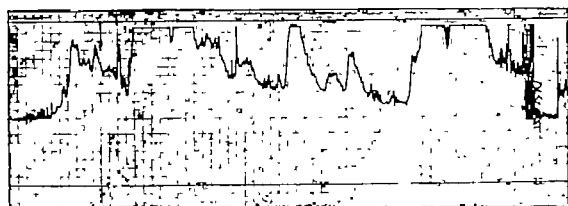


Fig. 4 "Hendren" reimplant with "anterior" clam.



Routine laboratory urodynamics



Extended night studies

Fig. 5 Normal laboratory urodynamic studies with phasic instability during night studies.

enuresis have had the bladder removed and a further segment of ileum used to form a "double clam". Both remain symptomatic, 1 with abnormal laboratory urodynamics and 1 wet only at night with normal urodynamics but abnormal night studies.

Discussion

The "clam" is the procedure of choice in both idiopathic and neuropathic detrusor dysfunction unless the bladder is so severely fibrotic and sacculated as to be unusable. Since it is usually not possible to predict those who will need to self-catheterise, every patient should be taught the technique pre-operatively and those in whom it is unacceptable should not undergo the procedure. It is also not possible to predict those patients who will have residual symptoms. However, the "double clam", preserving the original segment, does not appear satisfactory and if unacceptable symptoms persist, a detubularised substitution cystoplasty must be preferable, accepting that SIC will almost certainly be required. The "clam" usually resolves the stress element of incontinence but a Pereyra procedure can be performed subsequently. Unlike

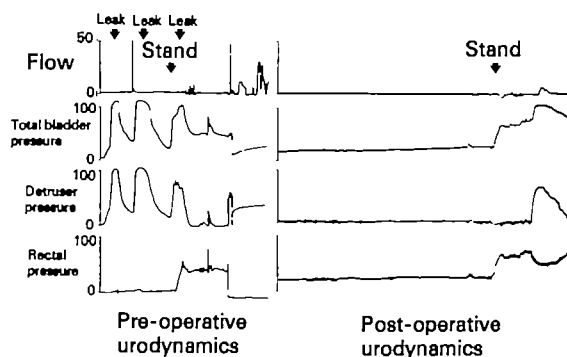


Fig. 6 Urodynamic studies before and after the "clam" in congenital instability.

transection and phenolisation, the "clam" has stood the test of time. In the small number with symptoms, these have persisted immediately after surgery and there have been no long-term relapses. The one doubt that remains is the possible long-term risk of tumour formation, which in our 2 cases (Stone *et al.*, 1987) was almost certainly related to stasis and chronic infection. Long-term follow-up and rigorous control of urinary tract infection is mandatory.

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Effect of Bladder Filling on Upper Tract Urodynamics in Man

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Summary—A group of 21 patients with hydronephrosis but normal bladders had their upper urinary tract pressures monitored while perfusing the affected kidneys through a fine bore nephrostomy tube, initially with the bladder on free drainage and subsequently during bladder filling. In 7 patients the renal pelvic pressures were altered by bladder filling and loin pain was reproduced in 4. It was concluded that with high upper tract flow rates, vesical filling can affect upper tract dynamics and this should be considered when evaluating patients with loin pain or potential obstructive uropathy.

In recent years diuresis renography (O'Reilly, 1986) and perfusion pressure flow studies (PPFS) (Whitaker, 1979) have proved invaluable in the critical evaluation of the dilated upper urinary tract. However, there remain a significant number of patients with loin pain and hydronephrosis in whom these urodynamic studies are either equivocal or normal.

Previous studies in patients with hydrouretero-nephrosis and a poorly compliant bladder have shown that upper tract dynamics are significantly altered by bladder filling (Jones *et al.*, 1988). The present study investigated whether vesical filling had any effect on upper tract drainage in patients with hydronephrosis and normal bladder compliance; such a concept, if proven, would help to explain some cases of idiopathic loin pain associated with equivocal standard urodynamic studies.

Patients and Methods

Twenty-one consecutive patients (13 male and 8 female), referred for PPFS to clarify their upper tract urodynamic status, were studied prospectively. All had unilateral hydronephrosis (16 pelvic-caliceal dilatation alone, 5 with additional

hydroureter) and either loin pain and/or impaired renal function. Two of those with a hydroureter had had a previous ureteric reimplantation. No vesicoureteric reflux was demonstrated.

All patients had a 7F nephrostomy tube inserted percutaneously under local anaesthesia. This was connected to a pressure transducer for recording renal pelvic pressure (RPP) and, via a side arm, to a syringe pump to allow upper tract perfusion at a fixed rate. All patients had a bladder pressure monitoring line connected to a pressure transducer and a separate urethral catheter to allow vesical filling and emptying during the course of the examination.

Patients lay supine on a radiographic couch and upper tract perfusion was performed using radiographic contrast media. This allowed intermittent fluoroscopy for the assessment of upper tract filling, peristalsis and pelvic ureteric and vesicoureteric transport.

Upper tract perfusion was initially performed at 10 ml/min with the bladder catheter on free drainage until an equilibrated RPP was obtained. Perfusion was then continued while the bladder was filled with normal saline at 100 ml/min. When the patient experienced a definite desire to void the vesical volume was held constant for 1 min and then the bladder was drained completely via the catheter. Upper tract perfusion was continued throughout. The effects of these manoeuvres on

RPP, patients' symptoms and fluoroscopic visualisation of upper tract peristalsis and emptying were recorded.

In patients who had a negative or equivocal RPP rise while perfusing the kidney at 10 ml/min the study was repeated while perfusing at 20 ml/min.

A rise in equilibrated RPP of less than 15 cm H₂O was considered non-obstructive and a rise greater than 22 cm H₂O was considered obstructive. Equilibrated RPP rises of 15 to 22 cm H₂O were considered to be equivocal.

Results

There were 16 patients who had pelvicaliceal dilatation alone. While perfusing at 10 ml/min 8 had an obstructive and 1 an equivocal PPFS which was uninfluenced by vesical filling. The remaining 7 patients had a non-obstructive PPFS. In 3 of these, bladder filling had no effect on RPP but in the other 4 some rise in RPP occurred while perfusing with a full bladder (Fig. 1). In no case, however, did this convert a non-obstructive to an obstructive pressure rise.

The 8 patients who did not have an obstructive

PPFS then had their upper tracts perfused at 20 ml/min. In 4 an obstructive pressure rise was seen with no bladder effect in 3, but in the fourth a further rise in RPP occurred when the bladder was filled. Four patients remained non-obstructive while perfusing at 20 ml/min with an empty bladder. In 2 cases no change was observed when the bladder was filled but in the other 2 phasic unstable bladder contraction waves were precipitated and corresponding intermittent rises in RPP were seen (Fig. 2). Neither patient experienced urgency or incontinence but loin pain was reproduced in one.

There were 5 patients with hydroureteronephrosis. While perfusing at 10 ml/min with an empty bladder 1 was obstructed. The other 4 were non-obstructed. Bladder filling had no effect on RPP in 1, another 1 became obstructed with a full bladder and 2 increased their renal pelvic pressures into the equivocal range while perfusing with a full bladder. These last 4 patients were also perfused at 20 ml/min. All 4 were non-obstructed while perfusing with an empty bladder. Vesical filling had no effect in 1 but the other 3 all converted to an obstructed PPFS when the bladder was filled (Figs 3 and 4).

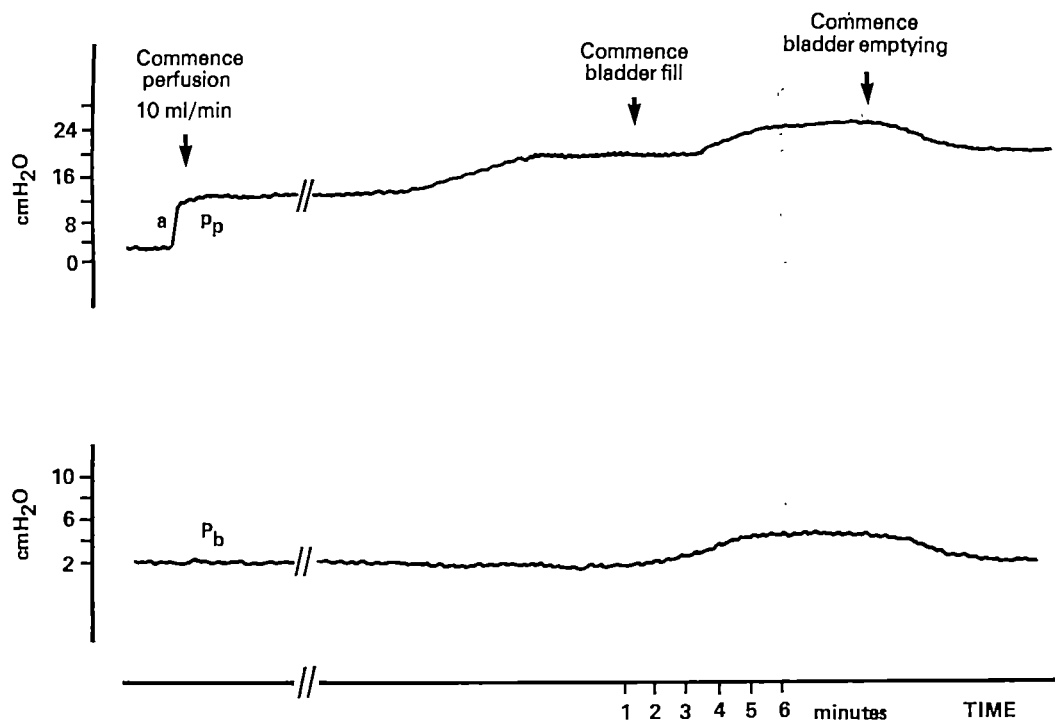


Fig. 1 Diagrammatic representation of upper tract perfusion pressure flow study in patient with pelvicaliceal dilatation. Perfusion at 10 ml/min, initially with bladder on free drainage and then during bladder filling. P_p = renal pelvic pressure. P_b = bladder pressure. Initial pressure rise a = pump artefact.

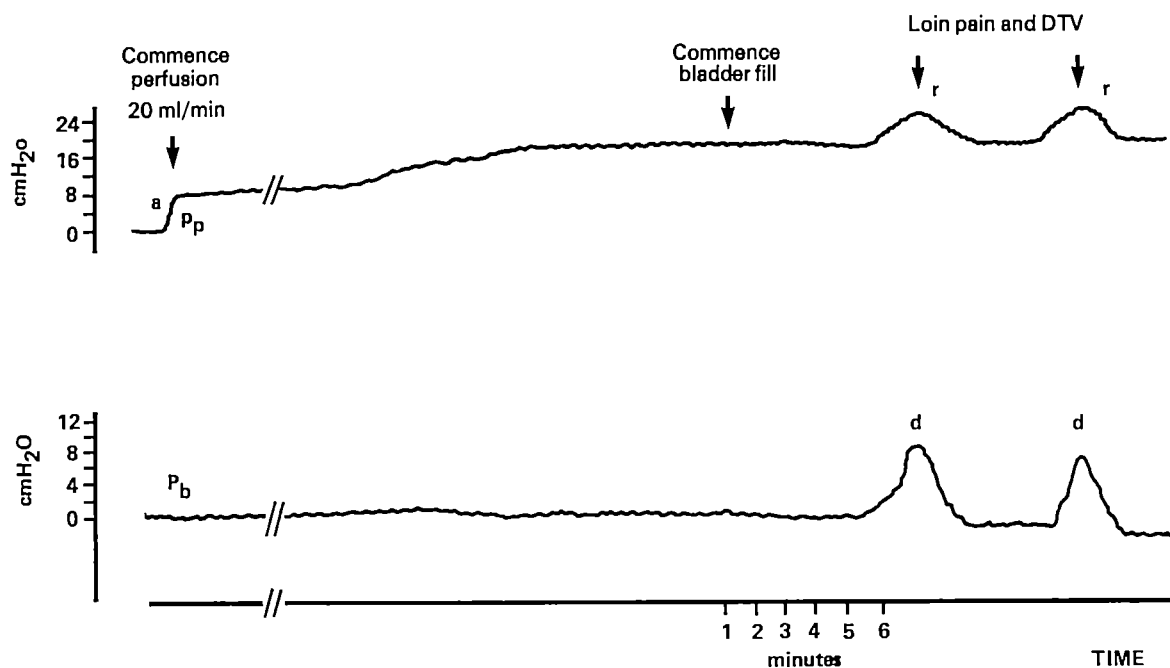


Fig. 2 Diagrammatic representation of upper tract perfusion pressure flow study in patient with pelvicaliceal dilatation. Perfusion at 20 ml/min, initially with bladder on free drainage and then during bladder filling. P_p =renal pelvic pressure. P_b =bladder pressure. Initial pressure rise a=pump artefact. Note phasic detrusor pressure rises (d) and associated increases in renal pelvic pressure (r) when the patient experienced a desire to void (DTV) and in 1 case loin pain.

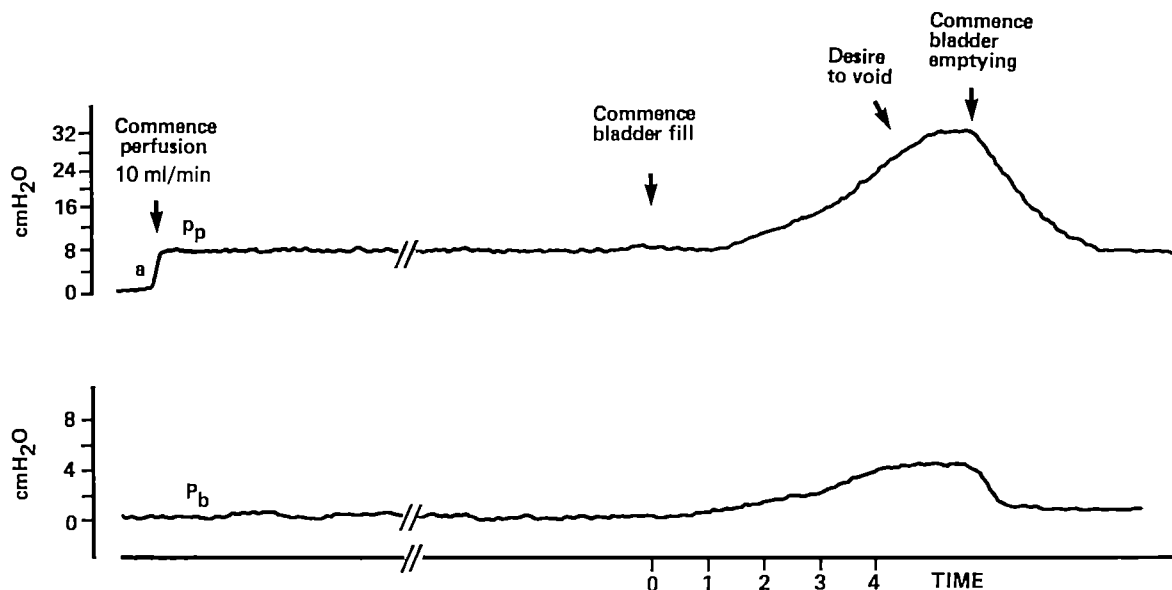


Fig. 3 Diagrammatic representation of upper tract perfusion pressure flow study in patient with hydroureteronephrosis. Perfusion at 10 ml/min, initially with bladder on free drainage and then during bladder filling. P_p =renal pelvic pressure. P_b =bladder pressure. Initial pressure rise a=pump artefact. Note that a non-obstructive study is converted to an obstructive pattern when the bladder is filled.

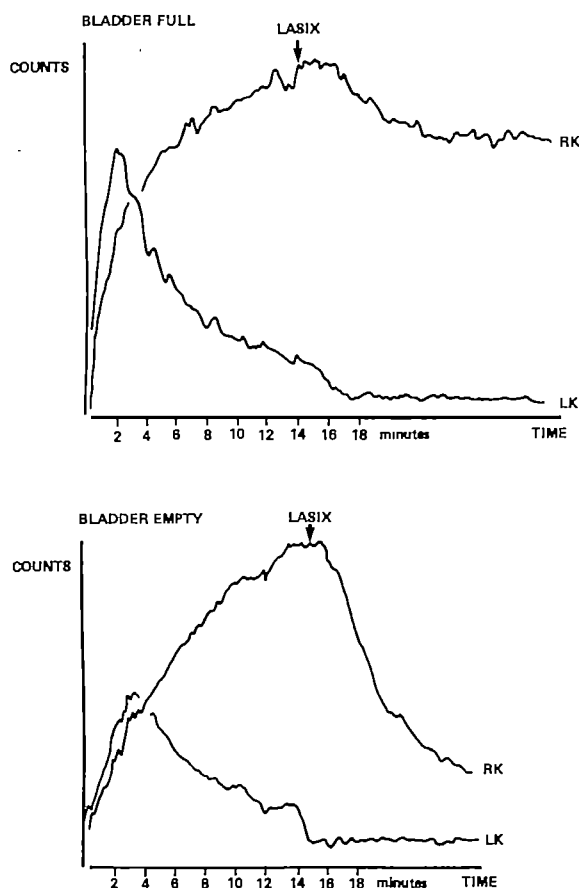


Fig. 4 ^{125}I Hippuran renograms from the same patient as illustrated in Figure 3. Note the obstructive excretion pattern when the bladder is full but satisfactory tracer washout when the bladder is emptied.

Overall, 7 of the 21 patients had their upper urinary tract pressures affected by bladder filling. Loin pain was reproduced at this point in the study in 4 of these.

Discussion

Previous reports, based on theoretical models and animal studies (Griffiths, 1987) and in patients with abnormal, poorly compliant bladders, have shown that the degree of vesical filling and intravesical pressure are crucial factors affecting upper tract drainage (George *et al.*, 1983 and 1984; Jones *et al.*, 1988; Styles *et al.*, 1988). The present study suggests that even with a normal bladder, vesical filling can influence upper tract dynamics.

With the presence of a hydroureter it is not difficult to envisage bladder filling having an effect on upper tract pressures. Under diuretic conditions,

after the initial filling of the dilated upper tract, flow is through an "open tube" system and when the outflow resistance, *i.e.* bladder pressure, is increased, then the renal pelvic pressure rises. This does not imply that vesicoureteric reflux is occurring, but suggests that there is equilibration of pressures across the vesicoureteric junction (Griffiths, 1987).

When a normal ureter intervenes between the bladder and dilated pelvicaliceal system, the effects of bladder filling are more difficult to explain. However, at high flow rates in the normal ureter, urine transport is no longer by peristalsis and "open tube" flow supervenes, once again allowing increased vesical pressures during bladder filling to have an effect more proximally (Griffiths, 1987). This kind of open tube flow was seen fluoroscopically during the present study.

This situation would seem unlikely to occur in patients with classic pelviureteric junction obstruction because limited pelviureteric fluid transport would presumably not allow high enough flows for "open tube" conditions to develop. Thus the present observations of the effects of bladder filling on RPP in patients with normal ureters and pelvicaliceal dilatation (as seen on a standard IVU with lower flow rates) may apply only to those with minor degrees of impedance to upper tract flow or may even be one extreme of the normal physiological spectrum.

Flow rates of 20 ml/min are higher than would normally occur under physiological conditions, but nonetheless such high flows can occur and have been recorded under extremes of alcohol or frusemide-induced diuresis (Lupton *et al.*, 1985). Thus the observations reported herein are thought to be those experienced when the system is stressed to the limits of normality. Nevertheless, they do explain some cases of idiopathic loin pain; in 4 of 21 patients the loin pain was reproduced during the investigation and 3 others had increased RPP which may conceivably have contributed to renal impairment. These patients have been successfully managed by simply advising regular moderate fluid intake combined with regular voiding.

Although this report deals with PPFS, the observation that bladder filling may affect upper tract drainage under conditions of marked diuresis is equally applicable to renography or intravenous urography.

We suggest that in patients with hydronephrosis and either loin pain which is difficult to diagnose or deteriorating renal function, in whom standard upper tract urodynamic studies are equivocal, the

studies be repeated with a full and then an empty bladder under the stimulus of high flow rates to clarify upper tract drainage. Some patients may be successfully managed by simple advice regarding moderate fluid intake and regular voiding.

Acknowledgement

We are grateful to Dr Pauline Sambrook for inserting the nephrostomy tubes and to all those clinicians who referred patients to us for evaluation.

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Disorders of Micturition in Tabes Dorsalis

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Summary—The aim of this study was to determine whether the disorders of micturition that occur in patients with tabes dorsalis can be attributed exclusively to disturbed bladder sensation, as has been previously suggested. Urodynamic studies were performed in 8 patients with tabes dorsalis who had no obvious organic obstructive urological disease. The results indicated that not only disturbed bladder sensation but also suprasacral and/or sacral lesions innervating the detrusor could be responsible for voiding dysfunction in such patients.

Voiding dysfunction is a well known feature of tabes dorsalis and in the past it was one of the commonest types of neurogenic bladder dysfunction (Gowers, 1893; Gill, 1936; Brodie *et al.*, 1939). Tabetic bladder is characterised by difficulty in urination and increased residual urine which could lead to urinary retention with overflow incontinence and atonic cystometrograms (Ruch, 1960; Otani *et al.*, Hald and Bradley, 1982; Adams and Victor, 1985). However, few urodynamic studies have been carried out to elucidate its features (Ertuck, 1987) and we therefore report the urodynamic findings in 8 patients with tabes dorsalis.

Patients and Methods

In recent years we have examined 10 patients with tabes dorsalis; 2 of them were excluded from this study because of significant benign prostatic hypertrophy. All 8 patients were male and their ages ranged from 36 to 75 years. The diagnosis of tabes dorsalis was based on clinical history and neurological and laboratory examinations. All had a previous history of venereal disease but only 1 (case 4) had been treated with penicillin. The clinical findings are summarised in Table 1. Although computed tomography showed cerebral atrophy in 3, and spinal X-ray showed cervical spondylosis in 4 and

lumber spondylosis in 5, none had corresponding clinical signs other than tabes dorsalis. Seven patients had a positive *Treponema pallidum* haemagglutinin test (TPHA) in serum and cerebrospinal fluid and 1 (case 7) had a positive TPHA only in serum. Rectal examination, retrograde urethrocytography and voiding cystourethrography revealed that no patient had significant obstructive urological disease. After a history of voiding symptoms was obtained, urodynamic studies were performed; they comprised uroflowmetry, measurement of residual urine, water cystometry, sphincter electromyography and voiding cystourethrography. Cystometry was performed with the patient in the supine position and a 14F bi-lumen urodynamic catheter was inserted transurethraly into the bladder. Aseptic distilled water at room temperature was instilled through one lumen at a flow rate of approximately 50 ml/min. The second lumen was used to measure intravesical pressure. A rectal catheter, held in the ampulla by an inflated balloon, was used to measure the intra-abdominal pressure. With the patient supine, the transducers were zeroed at the level of the symphysis pubis. These pressures were displayed on Life-Tech Instruments' Model 1154 or Nihon-Koden's strip chart recorders. Sphincter electromyography was performed using needle electrodes in the perineal striated muscles. The electromyographic potentials were studied on a loudspeaker and oscilloscope and recorded on the strip chart recorder.

Table 1 Clinical Features of 8 Male Patients with *Tabes Dorsalis*

	<i>Case no. (age (years))</i>							
	<i>1 (36)</i>	<i>2 (66)</i>	<i>3 (57)</i>	<i>4 (64)</i>	<i>5 (70)</i>	<i>6 (75)</i>	<i>7 (62)</i>	<i>8 (72)</i>
Initial symptom	Visual symptom	Pain in L.E.	Pain in L.E.	Ataxic gait	Pain in L.E.	Pain in L.E.	Con-vulsion	Pain in L.E.
Duration from initial symptom	3 months	5 years	8 years	10 years	10 years	15 years	28 years	32 years
Acute pain	—	+	+	—	+	+	—	+
Ataxic gait	+	—	—	+	—	+	+	+
Romberg's sign	+	—	—	+	—	+	+	+
Loss of knee jerk	+	+	+	+	+	+	+	+
Deep sensory loss	+	+	+	+	+	+	+	+
A-R pupil	+	—	+	—	+	—	+	+
Optic atrophy	+	—	—	—	—	—	—	—
Charcot's joint	—	—	—	—	—	—	+	—
Cerebral atrophy	—	—	—	+	—	+	+	—

L.E. = Lower extremities. A-R pupil = Argyll Robertson pupil.

Results

The case histories revealed that 7 patients had urinary symptoms; they were obstructive in 2, irritative in 3 and 2 patients had both types of symptoms. One patient (case 7) was suffering from urinary retention and 3 had urge incontinence (Table 2). Uroflowmetry was performed in 5 patients and 2 showed abnormal maximum flow rates or average flow rates according to the nomogram (Siroky, 1980). Residual urine was measured in all patients except for the one with urinary retention. Two patients had 30 ml and the rest had no residual urine. Cystometry was performed in all cases and

the results are shown in Table 3. The detrusor was overactive in 5 patients (phasic type in 3 and tonic type in 2) and normal in 3. A bladder capacity at first desire to void of <100 ml and >300 ml, and a maximum cystometric capacity of <200 ml and >600 ml, were considered abnormal according to our experience. The results showed that 6 patients had increased and 2 had normal bladder capacity at first desire to void; 3 had increased and 5 had normal bladder capacity at maximum cystometric capacity. In only 1 patient was high compliance found. Sphincter electromyography revealed 2 patients with detrusor-sphincter dyssynergia. The bulbocavernosus reflex was brisk in 1 patient, decreased in 1 and normal in 6. Voiding cystourethrography was performed in all patients except for the one with urinary retention and all showed opening of the bladder neck.

Table 2 Urinary Symptoms

	<i>Case no.</i>							
	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>
Obstructive	+	+	—	—	—	+	+	—
Irritative	—	—	—	+	+	+	+	+
Incontinence	—	—	—	+	—	—	+	+

* Urinary retention.

Discussion

Tabes dorsalis was a common disease until the advent of penicillin. However, as with our patients, this disease can still occur when such treatment is

Table 3 Results of Cystometry

	<i>Case no.</i>							
	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>
FDV (ml)	320*	360*	200	310*	400*	310*	400*	240
MCC (ml)	>600*	530	310	390	500	360	>600*	>600*
Curve	High compliance	Normal	Normal	Overactive (phasic)	Overactive (phasic)	Overactive (tonic)	Overactive (phasic)	Overactive (tonic)

FDV = First desire to void. MCC = Maximum cystometric capacity.

* = Increased capacity.

either not given or is inadequate. In the present series, 7 patients had urinary symptoms which confirmed that voiding dysfunction is common among patients with tabes dorsalis (Gowers, 1893; Gill, 1936; Brodie, 1939). The characteristic voiding dysfunction was said to be an atonic bladder with a large volume of residual urine due to loss of bladder sensation secondary to posterior root and posterior column lesions (Ruch, 1960; Otani *et al.*, 1980; Hald and Bradley, 1982; Adams and Victor, 1985). Our results showed that 6 patients had increased cystometric capacity at first desire to void and 3 patients also had increased maximum cystometric capacity, indicating that disturbed bladder sensation is common. This is in accordance with previous reports. Although no clear details of urinary symptoms are given in the literature, our results show that irritative and obstructive symptoms occur with almost equal frequency. Irritative symptoms such as urgency, frequency and urge incontinence are usually attributed to abnormal storage function but could also occur in the bladder with residual urine due to disturbed evacuation. In our patients, however, only 1 had urinary retention and the remainder had no or minimum residual urine. Therefore most of our patients' irritative symptoms seem to have been caused by disturbed storage function.

The tonic type of detrusor overactivity, which was noted in 2 patients, consisted of a steady rise in detrusor pressure with low compliance, and this has also been reported in 2 of 4 patients with tabes dorsalis by Otani *et al.* (1980). On the other hand, the phasic type of detrusor overactivity, which we noted in 3 patients, has not been described previously. Although both types of detrusor overactivity can be caused not only by neurological but also by non-neurological disorders, in the absence of significant obstructive urological disease in our patients, we favour a neurological origin. The neurological sites responsible for detrusor overactivity of the tonic type seem to be in the spinal cord conus or cauda equina (Murnaghan *et al.*, 1979; Snape *et al.*, 1987) and for the phasic type they seem to be located in suprasacral lesions. The typical pathological lesions of tabes dorsalis lie in the posterior roots and posterior columns but other areas of the spinal cord may also be involved

(Schmidt and Gonyea, 1986). Thus it is possible that our patients' cystometric abnormalities were due to tabes dorsalis *per se*. Other factors contributed to age-related subclinical lesions, such as cerebral atrophy, cervical spondylosis or lumbar spondylosis, cannot be ruled out. It is concluded from this study that voiding dysfunction in tabes dorsalis is due not only to abnormal bladder sensation, as is generally believed, but also to detrusor overactivity even after the exclusion of obstructive urological disease.

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The Intraprostatic Spiral. New Treatment for Urinary Retention

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Summary—In a series of 45 consecutive patients with acute or chronic urinary retention, 41 were treated by insertion of an intraprostatic spiral using ultrasonic guidance under local anaesthesia. Insertion was successful in 35 patients and in 6 the spiral was inserted endoscopically.

During a follow-up period of 12 months 8 patients died, all with a functioning spiral. The device was removed in 16 patients; in 6 cases the reasons for removal were related to the spiral and in 10 they were not. The spiral remained *in situ* in 17 patients and all had satisfactory voiding. This device is a good alternative to an indwelling catheter in patients awaiting prostatic surgery and also in those who are either unfit or unwilling to undergo prostatectomy.

The currently accepted treatment for symptomatic benign prostatic hypertrophy (BPH) is transurethral prostatectomy (TURP). This operation has a subjective and objective success rate of about 90% and low morbidity and mortality (Chilton *et al.*, 1978; Abrams *et al.*, 1979). The optimal treatment for BPH includes an assessment of the symptomatology and general medical condition of the patient plus critical assessment of relative efficacy and morbidity. Patients with BPH are elderly and often have other severe disorders. Thus many attempts have been made to develop non-surgical treatment for BPH. These include administration of α -adrenergic blockers, surgical and medical castration and mechanical or balloon dilatation of the prostatic urethra. The clinical efficacy of these options is based upon preliminary clinical observations (Lepor, 1989). Recently, the endoscopically inserted intraprostatic spiral (Fabian, 1980, 1984; Fabricius *et al.*, 1983; Flier and Seppelt, 1987; Langkopf *et al.*, 1981; Reuter and Dettinger, 1986; Røhl *et al.*, 1987; Schöps and Kierfeld, 1987) and the ultrasonically guided transurethral intraprostatic spiral (Nordling *et al.*, 1989) have been introduced for the treatment of BPH. The latter

procedure and the results of early follow-up have already been reported by Nordling *et al.* (1989). The aim of this study was to evaluate the results after 12 months' follow-up.

Patients and Methods

The series comprised 45 consecutive patients (range 50–93 years, median 77) with acute or chronic urinary retention supposedly due to benign prostatic hyperplasia; 41 were treated with an intraprostatic spiral (Fig. 1). Patients with prostatic carcinoma or urethral stricture were excluded. The catheterisation period prior to insertion ranged from 1 day to 8 years (median 9 days). The volume of residual urine was known in 25 patients and ranged from 200 to 2500 ml (median 1000). Twenty-five patients had severe complicating cardiopulmonary or neurological disorders. The bladder was filled with 150 to 300 ml of 0.01% chlorhexidine and the prostatic urethral length was measured by transabdominal ultrasonic scanning after scanning of the bladder to exclude tumours and stones (Fig. 2). A spiral 10 to 15 mm longer than the prostatic urethral length was chosen to ensure that the tip of the spiral was inside the bladder and it was inserted under sterile conditions as for normal catheterisation. Advancement of the spiral and its correct positioning were

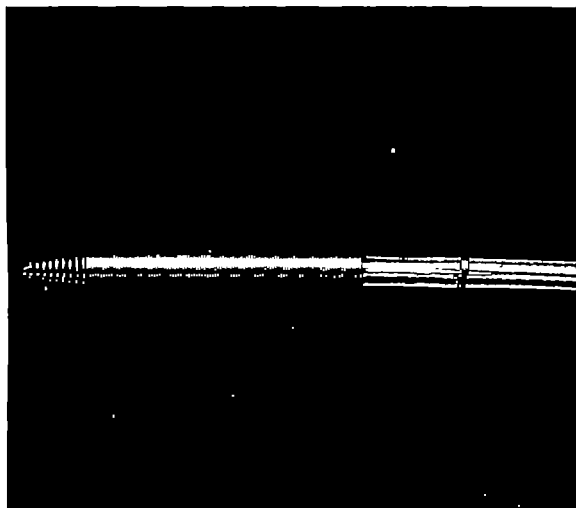


Fig. 1 The intraprostatic spiral.

controlled by transabdominal ultrasonic scanning (Fig. 3).

All patients were given antibiotic prophylaxis (either oral ampicillin or trimethoprim) for 48 h, starting just before insertion. Further antibiotic treatment was prescribed only in the case of significant bacteriuria.

Insertion was successful in 35 patients (78%, 95% confidence limits 63–89%). In 10 patients the spiral was caught in the prostate. In 6 of these the device was inserted endoscopically and in the other 4 cases no further attempts were made.



Fig. 2 Transabdominal ultrasound scan of bladder and prostate. Balloon catheter *in situ*. + — × denotes distance from bladder neck to apex of prostate (35 mm).

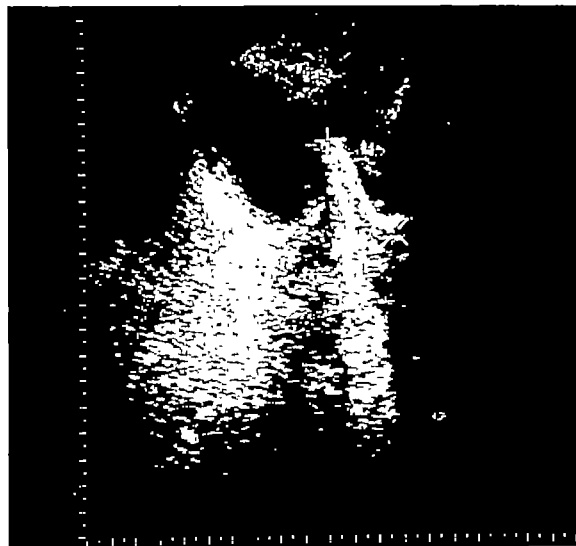


Fig. 3 Transabdominal ultrasound scan showing spiral *in situ*. + — × denotes length of body of spiral (45 mm).

Results

During the 12-month follow-up period 8 patients died, all with a functioning spiral (Table 1, Fig. 4). Dislocation of the spiral occurred between 1 and 162 days (median 8) after insertion. In 11 cases the device was repositioned and in 4 it was removed because of recurrent dislocation. The time to removal is shown in Figure 4 and the reasons for removal in Table 2. A total of 16 patients had the spiral removed but in only 6 cases were the problems related to the device: recurrent dislocation (4), persistent bacteriuria and urgency (1) and local perineal discomfort (1). Slight encrustation was noted on the tip of 1 spiral.

One patient, satisfied with the spiral, was admitted with severe haematuria. The spiral was removed and TURP performed, following which he had 3 further episodes of haematuria, the cause of which could not be found. Although satisfied with the spiral, 1 patient requested a prostatectomy. After 9 months another patient, also satisfied with the spiral, was diagnosed as having prostatic cancer and bone metastases. Suspicion was aroused because of low back pain. Orchiectomy was performed and the spiral was later removed with maintenance of satisfactory micturition. The last 7 patients underwent TURP but haematuria and urgency (1 patient), urinary retention (3) and urge incontinence (3), which had been present during treatment with the spiral, persisted after the resection.

There was no difference in age, prostatic length and residual urine between patients with the spiral

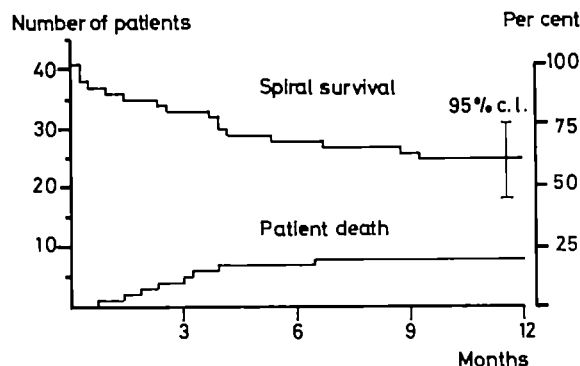


Fig. 4 Time to removal of spiral and number of deaths in 41 patients.

in situ at follow-up and those with the spiral removed. Seventeen patients still had the spiral at the 12-month follow-up appointment. Although some of these had voiding symptoms (Table 3), all were satisfied with the spiral and had satisfactory subjective voiding.

Uroflowmetry was performed in all patients, but not at every follow-up visit (Table 4). Statistical calculations were not performed, mainly due to the large differences in the number of patients at follow-up. However, the results indicated a decrease in the maximal flow rate over time with almost unchanged voided volumes.

Table 1 Follow-up of 41 Patients with Urinary Retention Treated with an Intraprostatic Spiral

12 months' follow-up	No. of patients
Spiral removed	16
Patient died with spiral <i>in situ</i>	8
Spiral <i>in situ</i> and voiding satisfactory	17

Table 2 Reasons for removal of Spiral

No. of patients	
4*	Recurrent dislocation
3	Detrusor insufficiency and urinary retention
3	Urge incontinence
1	Persistent haematuria and urgency
1*	Persistent urinary tract infection and urgency
1*	Local perineal discomfort
1	Acute severe haematuria
1	Although satisfied with the spiral the patient wanted a prostatectomy
1	Prostatic cancer and bone metastases followed by orchiectomy

* Failures related to the spiral.

Table 3 Voiding Symptoms in 17 Patients with Subjective Satisfactory Voiding

Symptoms	No. of patients
Diuria (<3 h)	2
Nocturia (>1)	2
Hesitancy	3
Weak stream	2
Urgency	2

Table 4 Results of Uroflowmetry

Follow-up	Median maximum flow rate (range) (ml/s)	Median voided volume (range) (ml)
0-14 days (n=32)	12.5 (2.0-35.0)	193 (50-663)
3 months (n=23)	13.6 (3.0-35.0)	220 (53-420)
6 months (n=13)	9.4 (1.0-21.3)	200 (73-400)
12 months (n=10)	8.5 (3.0-26.0)	215 (100-490)

Twelve patients had significant bacteriuria before insertion of the spiral. The day after insertion 1 patient developed septicaemia. Persistent bacteriuria was present in 3 patients. One of these had the spiral removed and 2 had no symptoms under long-term low-dose antibiotic prophylaxis. During follow-up only 4 of the 29 patients with sterile urine prior to insertion had 1 episode of asymptomatic bacteriuria.

Discussion

Ultrasonically guided, transurethral insertion of an intraprostatic spiral is a rapid and straightforward procedure with a high success rate. Our experience shows that all spirals can be inserted into the prostatic urethra using a 7F ureteric catheter as a guidewire (Fig. 5).

The spiral became dislocated and was repositioned in 11 patients, but repositioning was permanently successful in only 7 patients. These dislocations occurred soon after insertion in 10 patients and in 1 case the spiral migrated after 162 days. If the spiral remains in the correct position during the first six weeks after insertion it will probably become fixed in the prostatic urethra and late dislocation is unlikely. If the position of the spiral is not optimal, or if dislocation does occur, correction can be carried out endoscopically.

In 16 patients the spiral was removed during follow-up, but in only 6 were the problems related to the spiral. In the other 10 patients the problems were related to their general condition and the



Fig. 5 Intraprostatic spiral mounted with a 7F ureteric catheter as a guidewire.

symptoms were unchanged after TURP. Voiding symptoms in patients with retention due to underactive detrusor function are seldom improved by outflow surgery (Abrams *et al.*, 1978; George *et al.*, 1986). It is possible that some of the patients whose spiral was removed were not candidates for treatment with the spiral or for TURP, but in most centres urinary retention is considered an absolute indication for prostatectomy.

The present study has shown that insertion of an intraprostatic spiral is a satisfactory method of treating urinary retention due to BPH. The patients were included consecutively in the study and more than half had severe cardiopulmonary or neurological disorders. This was emphasised by the high mortality in the follow-up period. The spiral also seems to be a good alternative to an indwelling catheter during the waiting period prior to prostatectomy.

Uroflowmetry probably showed a decrease in the maximal flow rate during the 12 months of follow-up. This may be attributed to encrustation on the spirals, which was found in 1 case. This spiral was removed after 18 weeks. Encrustation will probably occur mainly during long-term treatment.

These complications do not prohibit long-term use. In patients with sterile urine prior to insertion, urinary tract infection is infrequent; in patients with bacteriuria, symptomatic infection may be prevented by low-dose antibacterial treatment. Haematuria and local perineal discomfort were rare. To date, there have been no urethral strictures.

We do not yet know the incidence of long-term

complications, especially the incidence of urethral strictures in patients who have the spiral in place for more than 1 year. The formation of encrustations on the spiral during long-term treatment might be indicated by recurrent voiding symptoms and reduced maximal flow rate. A new spiral could then be inserted.

Until we know the type and incidence of long-term complications, we recommend that the spiral be used only in patients with urinary retention (1) in the waiting period prior to prostatectomy, (2) when the patient is unwilling to undergo prostatectomy and (3) in cases where the operative risk is too high.

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Pituitary Adrenal and Gonadal Endocrine Suppression for the Primary Treatment of Prostate Cancer

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Summary—Sixty new patients with advanced local or metastatic prostatic cancer were randomised to receive either bilateral orchiectomy, orchiectomy plus dexamethasone 0.5 mg in the morning and 0.3 mg at night, or orchiectomy plus cyproterone acetate 100 mg 3 times per day. All surviving patients have been followed up for a minimum of 2 years. An improvement in both objective and subjective responses in patients receiving dexamethasone compared with those receiving cyproterone acetate suggests a possible additional role for the pituitary in the control of prostatic tumour growth. A larger study with longer follow-up may be indicated.

Endocrine therapy for the treatment of advanced prostatic cancer has been available for over 40 years. Despite many improvements in such therapy, there is still at best a 60% objective response rate with no convincing evidence of any increase in survival for those who present with metastatic disease.

Most therapies have been aimed at suppression of the testicular production of testosterone using oestrogens or orchiectomy and more recently by the use of LHRH analogues (Allen *et al.*, 1983). Additional androgen suppression aimed at blocking the action of androgens produced by the adrenals and by peripheral conversion of precursor steroids has been attempted using a combination of an LHRH analogue or orchiectomy with an anti-androgen (Labrie *et al.*, 1985). Such attempts have been associated with an increased early response rate and at 3 years an improvement in the median time to disease progression compared with single conventional therapy (Garnick, personal communication).

It has been clearly shown that pituitary ablation, either by surgery or some form of radiotherapy, produces significant subjective improvement, particularly pain relief, in the majority of patients with

carcinoma of the prostate in whom the disease has relapsed after conventional endocrine ablation (Fitzpatrick *et al.*, 1980). The mechanism of this response is unclear and may be due to the suppression of some as yet unidentified hormonal peptides. In addition, mechanisms of control of adrenal androgen secretion are not fully understood (Anderson, 1980). There may be other pituitary factors which affect androgen production, particularly in the pre-pubertal period (Harding, 1979), and in some conditions there is a disassociation between adrenal androgen and cortisone secretion (Grumbach *et al.*, 1978; Parker and Odell, 1979).

To examine whether endocrine suppression aimed at the pituitary and gonadal axis has any significant additive value compared with androgen suppression aimed solely at the testes or testes, adrenals and peripherally produced androgens, a prospective randomised study was carried out to compare orchiectomy versus orchiectomy plus dexamethasone, orchiectomy plus cyproterone acetate or orchiectomy plus ketoconazole in patients with locally advanced or metastatic prostatic cancer.

Following the manufacturer's advice as to a significant incidence of septicæmia following high dose ketoconazole therapy, this arm of the study was withdrawn after 16 months and these patients are reported in a separate study. The remaining 3

groups of patients have now completed 2 years' follow-up and are the subject of this report.

Patients and Methods

Sixty new patients with advanced local or metastatic prostate cancer were randomised using random number tables to receive either bilateral orchiectomy, orchiectomy plus dexamethasone 0.5 mg in the morning and 0.3 mg at night, or orchiectomy plus cyproterone acetate 100 mg 3 times per day. Pre-operative staging and follow-up examinations were carried out at regular intervals and included clinical examination, digital rectal examination, serum acid phosphatase (total and tartrate labile) and radio-isotope bone scans. In addition, the following serum endocrine studies were performed at each visit: testosterone, dihydrotestosterone, androstenedione, progesterone, cortisol and luteinising hormone. Patients were evaluated objectively at 1 and 2 years using British Prostate Group criteria (Chisholm and Beynon, 1982).

Statistical methods

Patients were categorised at 2 years as responders, stable, progressing, dead from progressive disease or dead from other disease. Their response was compared between the 3 treatment groups using the Kruskal-Wallis one-way analysis of variance by ranks (adjusted for ties), using the statistical software package Minitab. The analysis was carried out both omitting the patients dead from other disease, and with these patients grouped with the patients dead from progressing disease. The 3 pairwise comparisons between groups were made by comparing the average ranks of the 3 groups, following the procedure given in Siegel and Castellan (1988) except that the adjustment for multiple comparisons they give (which in this case would effectively mean multiplying each *P* value by 3) was not used. All comparisons were made by two-tailed tests, with the level of significance being taken as 5%. Statistical analysis of the endocrine data was carried out using the unpaired Student's *t* test.

Table 1 Details of Patients

	No. of patients	Age range (years)	Age (mean)	Tumour grade			Metastatic	Elevated acid phosphatase
				1	2	3		
Orchiectomy	24	48-84	72	5	4	15	16	12
Orchiectomy + cyproterone acetate	20	54-84	74	6	4	10	16	13
Orchiectomy + dexamethasone	16	62-86	73	3	5	8	14	10

Details of patients are shown in Table 1.

Results

Endocrine studies

Serum testosterone was at all times lower in the group receiving dexamethasone but these differences were not significant (Fig. 1). There were no differences in serum dihydrotestosterone between the 3 groups of patients. The reduction in serum androstenedione in the orchiectomy plus dexamethasone group compared with the orchiectomy group was significant ($P < 0.001$) at 12 and 24 months (Fig. 2). In the group receiving cyproterone acetate the reduction in androstenedione at 24 months compared with the orchiectomy group was significant ($P < 0.02$). The reduction in serum cortisol in the group receiving dexamethasone was significant compared with the orchiectomy group at 12 and 24 months ($P < 0.001$) (Fig. 3). Although serum progesterone was reduced in the group receiving dexamethasone compared with the other 2 groups, these differences were not significant. The reduction in serum LH in the group receiving cyproterone acetate was significant at 12 months ($P < 0.001$) compared with the other 2 groups but not significant at 24 months (Fig. 4).

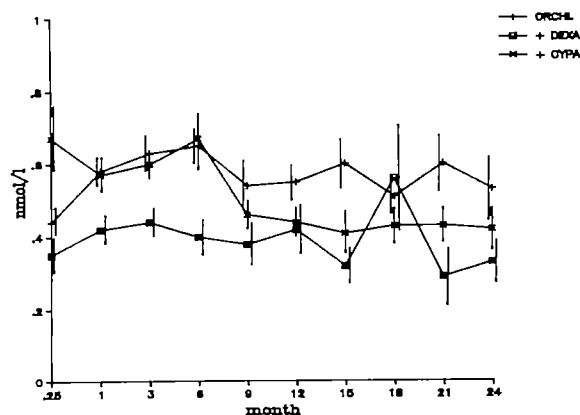


Fig. 1 Serum testosterone in the 3 treatment groups. Each bar represents the standard error of the mean.

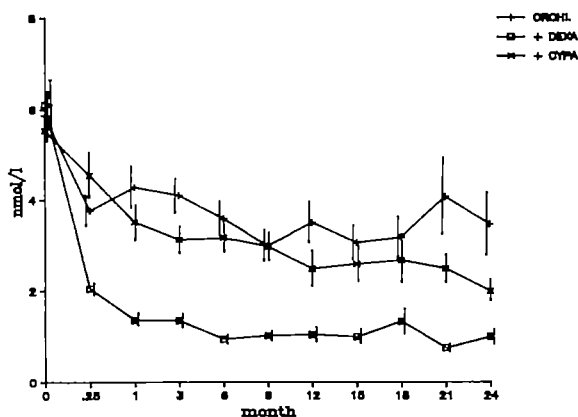


Fig. 2 Serum androstenedione in the 3 treatment groups. Each bar represents the standard error of the mean.

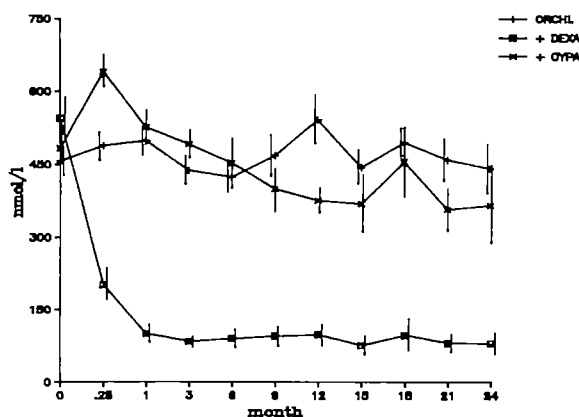


Fig. 3 Serum cortisol in the 3 treatment groups. Each bar represents the standard error of the mean.

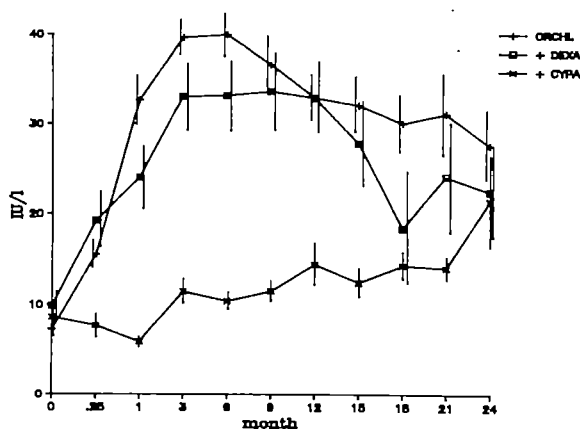


Fig. 4 Serum LH in the 3 treatment groups. Each bar represents the standard error of the mean.

Objective response

The response to treatment at 1 and 2 years is shown in Tables 2 and 3. At 1 year, 2 patients had died from carcinoma of the prostate in the orchiectomy group, 1 at 2 months and the other at 9 months. By 2 years, an additional 2 patients had died of prostatic cancer, both at 18 months. No patient in the orchiectomy group died from intercurrent disease. In the first year, 2 patients in the cyproterone acetate group died from prostate cancer, 1 at 2 and 1 at 9 months. In addition, 2 patients died, 1 from a myocardial infarct and congestive cardiac failure at 4 weeks and the other from respiratory failure at 6 months. In the second year, a further 3 patients died from prostate cancer at 16, 19 and 20 months and 1 patient died at 17 months from congestive cardiac failure. No patient died from prostate cancer at 1 year in the dexamethasone group but 1 died from a ruptured aortic aneurysm at 3 months. In the second year, 2 patients died from prostate cancer at 15 months and 1 from the myocardial infarct at 18 months. At 2 years, when patients dead from other diseases are omitted, the dexamethasone group performed significantly better than the cyproterone group ($P=0.0088$). Neither of the other 2 comparisons was significant, though the one between the orchiectomy and the orchiectomy plus dexamethasone groups was nearly so ($P=0.076$). When patients dead from progressing disease are included with those dead from other disease, orchiectomy plus dexamethasone gave a significantly better performance than orchiectomy plus cyproterone ($P=0.017$). Neither of the other 2 comparisons was significant.

Side effects of treatment

No patient in the orchiectomy group complained of unexpected side effects. In those randomised to cyproterone acetate, 1 patient who died at 16 months of prostatic cancer stopped treatment between 10 and 13 months because of lethargy. One stopped at 6 months for no apparent reason and died at 20 months from prostate cancer. One patient stopped at 12 months for no apparent reason and had progressive disease at 24 months. A further patient stopped treatment at 12 months because of thromboembolic complications and had stable disease at 24 months. All patients receiving dexamethasone gained weight and had an improvement in appetite and well-being. One patient who complained of gastrointestinal discomfort stopped therapy between 7 and 10 months and showed responding disease at 24 months.

Table 2 Results at 1 Year

	Group no.	Responders	Stable	Progressing	Dead from other disease	Dead from progressive disease
Orchiectomy	24	8	9	5	0	2
Orchiectomy + cyproterone acetate	20	9	6	1	2	2
Orchiectomy + dexamethasone	16	10	3	2	1	0

Table 3 Results at 2 Years

	Group no.	Responders	Stable	Progressing	Dead from other disease	Dead from progressive disease
Orchiectomy	22	7	6	7	0	2
Orchiectomy + cyproterone acetate	16	3	3	6	1	3
Orchiectomy + dexamethasone	15	10	1	1	1	2

Discussion

The majority of prostate cancers consist of a mixture of cells, some of which require the presence of androgens for their continued growth and some which do not. The suggestion by Labrie *et al.* (1985) that complete androgen suppression using an LH/RH analogue or orchiectomy plus an anti-androgen should result in improvements in survival and response rates was not initially supported by the results of randomised trials carried out by other workers. However, the Leuprolide study group has now completed a 3-year follow-up of patients randomised to either single therapy with the LH/RH analogue Leuprolide or total androgen ablation. Their results show an improved initial response rate for those randomised to total androgen ablation and also an improvement in the median time to disease progression (Garnick, personal communication).

The present study is the first to report attempts to inhibit androgen production further by pituitary suppression using dexamethasone. Serum testosterone was at all times lower in the group receiving dexamethasone compared with the other groups but this difference was not significant. However, the very marked reduction in serum androstenedione and serum cortisol in the dexamethasone group was highly significant at all time intervals (Figs 2 and 3).

Since the pituitary control of adrenal androgen production is not fully understood, the pituitary suppression induced by dexamethasone might also have suppressed other as yet unidentified hormone peptides.

The 3 treatment groups were very similar with regard to patients' age, number of poorly differentiated tumours, patients with metastatic disease and with an elevated acid phosphatase. All have now been followed up for a minimum of 2 years. In that time 4 patients in the orchiectomy group died from progressive disease and none from intercurrent disease; although 20 of the 24 patients are still alive, only 7 are showing evidence of disease response and 7 have progressive disease. In the group receiving cyproterone acetate, 5 died from progressive prostate cancer and 3 from cardiorespiratory failure. Of the survivors, 6 show progressive disease and only 3 evidence of disease response. In those receiving dexamethasone, 2 have died from prostate cancer and 2 from cardiovascular causes but of the 12 patients alive at 2 years only 1 shows progressive disease and 10 show evidence of disease response—a much higher proportion than in the other 2 groups. Statistical analysis has shown that the 3 groups did not have the same response irrespective of whether the patients who died from other diseases were omitted or included. In both analyses the group receiving orchiectomy plus dexamethasone showed responses which were significantly better than those of the orchiectomy plus cyproterone group. When patients dead from other diseases are omitted, the comparison between orchiectomy and orchiectomy plus dexamethasone was nearly significant ($P=0.076$). However, when patients dead from progressive disease are included with those who died from other diseases, the P value does not approach significance.

The safety of orchiectomy as a primary treatment for prostate cancer has again been shown, as has

an incidence of cardiovascular deaths in patients receiving cyproterone acetate. The improvement in both objective and subjective responses in patients receiving dexamethasone and the absence of any significant toxicity are of interest and suggest a possible additional role for the pituitary in the control of prostatic tumour growth.

This study suggests a role for dexamethasone in the primary treatment of prostatic cancer but a much larger study with a longer follow-up is required before any definite conclusion can be reached.

Acknowledgement

We acknowledge the help of Neil Alexander, Department of Medical Physics, for the statistical analysis.

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Gamma-seminoprotein—a New Tumour Marker in Prostatic Cancer?

Results of a Pilot Study

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Summary—Serum levels of gamma-seminoprotein (GSM), prostate specific antigen (PSA) and prostate specific acid phosphatase (PAP) were examined, using enzyme immunoassay, in 250 patients with prostatic disease. The results indicated that the highest specificity was obtained with GSM (94%) and the lowest with PSA (60%). In contrast, the highest sensitivity in newly detected carcinomas ($n=41$) was obtained with PSA (71%), whereas that of GSM (51%) was comparable to that of PAP (44%). Of 41 patients with newly detected prostatic cancer, 35 (85%) showed a significant increase in at least 1 of the tumour markers. Five of 6 patients whose markers were within normal limits had incidental carcinomas. During follow-up, PSA was raised in 88%, GSM in 66% and PAP in 55% within 12 months prior to clinical progression. Our results suggest that the determination of GSM may be of value in the serological detection and monitoring of prostatic cancer. These findings must be confirmed by further studies with larger numbers of patients and longer follow-up.

A seminal plasma glycoprotein (molecular weight 23 kD) was isolated by Hara *et al.* (1966) and was named gamma-seminoprotein because of its electrophoretic migration with the gammaglobulin fraction. Subsequently, immunohistological study of the prostate demonstrated the origin of this protein (Yamaguchi *et al.*, 1986). Okabe *et al.* (1982) measured GSM in serum by means of radioimmunoassay and concluded that this protein was a potential marker for prostatic cancer. Eto *et al.* (1985) reported the serum levels of GSM as measured by an enzyme immunoassay. An overall sensitivity of 68% and specificity of 90% were revealed when the cut-off level was defined as 4 ng/ml. However, Siddall *et al.* (1986) and Ercole *et al.* (1987) did not consider that GSM should be recommended as a diagnostic agent. More recently, Matsouka *et al.* (1988) and Arai *et al.* (1988) (unpublished material) showed GSM to be a good marker for prostatic cancer.

The aim of the present study was to compare the tumour markers prostate specific antigen (PSA) and prostate specific acid phosphatase (PAP) with the serum levels of GSM in patients with prostatic disease and to establish whether further studies were justified in order to improve the reliability of serological tumour markers.

Patients and Methods

Serum levels of GSM, PSA and PAP were evaluated in 88 patients with benign prostatic hyperplasia (BHP), in 41 patients with newly detected prostatic cancer (PCA) and in 121 patients with prostatic cancer treated by hormonal therapy (orchiectomy or LHRH analogue and/or cyproterone acetate, flutamide, estramustine phosphate). At the time of marker determination, 27 of these 121 patients demonstrated clinical progression (according to the criteria of the EORTC). All blood samples were taken after a 5-day interval from rectal palpation.

Serum assays were carried out in the same laboratory using "GSM-Chugai" (Chugai Pharmaceutical Corporation Ltd, cut-off level 4 ng/ml), the "Tandem-E-PSA immunoassay" (Hybritech Inc., cut-off level 4 ng/ml) and the "PAP-EIA" (Abbott Diagnostic Division, cut-off level 2.2 ng/ml). The cut-off level for GSM was 4 ng/ml, according to the results of Eto *et al.* (1985).

These assays were assessed with respect to specificity and sensitivity using samples from patients with BPH and from patients with newly detected prostatic cancer. The parameters were as follows:

Specificity = percentage of negative levels in patients with benign prostatic hyperplasia.

Sensitivity = percentage of positive levels in patients with newly detected prostatic cancer.

Results (Table 1, Fig. 1)

GSM

All but 5 patients with BPH were within the normal range (specificity = 94%), whereas pathological levels were detected in 21/41 patients with newly detected prostatic cancer (sensitivity = 51%); 10/20 patients with normal serum levels had an incidental carcinoma.

Elevated GSM was found in 16/27 patients (59%) with progression under therapy and in only 10/94 (10.6%) with stable disease.

PSA

Fifty-three patients with BPH had normal PSA levels (specificity = 60%); 35/41 patients with untreated cancer showed an increased value for PSA (sensitivity = 71%). In 5/12 patients with normal PSA levels an incidental carcinoma was found.

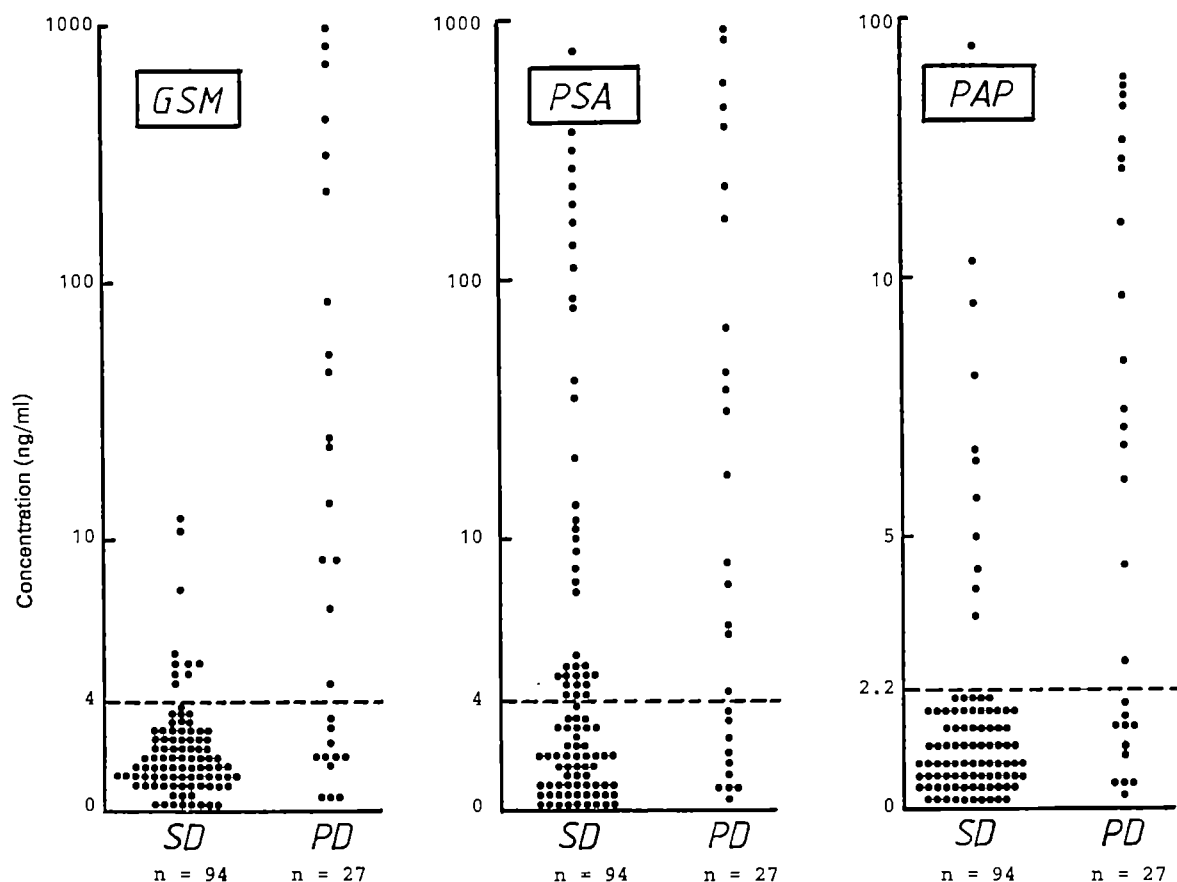


Fig. 1 Distribution of GSM, PSA and PAP levels in patients with progressive (PD) or stable disease (SD).

Table 1 Mean and Range of GSM, PSA and PAP with Regard to Stage and Grade in 41 Patients with Newly Detected Prostatic Carcinoma

Clinical stage		No. of patients (%)	GSM		No. of patients (%)	PSA		No. of patients (%)	PAP		No. of patients (%)
			Mean (ng/ml)	Range (ng/ml)		Mean (ng/ml)	Range (ng/ml)		Mean (ng/ml)	Range (ng/ml)	
T0A1	M0	8 (19.5)	0.93	0.0–1.7	0 (0)	3.16	0.3–6.2	4 (50)	0.73	0.2–1.2	0 (0)
	M+										
T0A2	M0	5 (12.1)	2.98	0.1–4.9	3 (60)	5.50	3.0–8.2	4 (80)	1.82	0.5–2.8	2 (40)
	M+										
T1	M0	6 (14.6)	3.05	0.9–5.8	2 (33)	5.50	0.9–14.5	2 (33)	1.31	0.5–3.1	1 (17)
	M+										
T2	M0	7 (17)	3.71	1.5–10.2	2 (28)	5.98	2.2–11.5	4 (50)	2.65	0.8–6.0	3 (42)
	M+	3 (7.3)	6.20	2.0–10.4	2 (67)	39.26	17.8–68	3 (100)	5.00	2.4–7.9	3 (100)
T3	M0	4 (9.7)	7.97	5.4–12.2	4 (100)	40.77	5.3–120	4 (100)	8.72	1.4–19.5	2 (50)
	M+	4 (9.7)	10.35	7.5–15.1	4 (100)	121.25	70–230	4 (100)	8.60	3.2–21	4 (100)
T4	M0										
	M+	4 (9.7)	14.32	12.0–17.5	4 (100)	578.5	82–1400	4 (100)	18.50	8.1–35	4 (100)
T0–T4	M0	30 (73)	3.28	0.0–12.2	11 (36)	9.69	0.3–120	18 (60)	2.54	0.2–19.5	8 (26.6)
	M+	11 (17)	10.65	3.5–17.5	10 (90)	265.16	17.8–1400	11 (100)	11.24	2.1–35	11 (100)

Elevated levels of PSA were found in 17/27 patients (62%) with clinical progression. Of 94 patients with stable disease, PSA was greater than 4 ng/ml in 30 (32%).

PAP

Only 25/88 patients with BPH showed false positive results (specificity = 71%) and 18/41 with untreated cancer had a true positive PAP (sensitivity = 44%). In 11/23 patients whose levels were within normal limits, an incidental carcinoma was observed; 11/94 patients (12%) with stable disease had elevated PAP, whereas an increase in this marker was found in 13/57 patients (48%) under progression.

False results regarding specificity and sensitivity are shown in Figure 2.

Follow-up data (Table 2)

Simultaneous evaluation (2-monthly) of all 3 markers was available in 35/94 patients who appeared to have clinically stable disease at the start of the assays. The mean levels for PSA, GSM and PAP were 3.56, 1.05 and 1.14 ng/ml respectively; the length of follow-up was at least 12 months.

Progression of disease occurred in 9 cases. On average, 9 months before clinical manifestation of progression, we found elevated PSA levels in 8/9 cases (median PSA 20.02 ng/ml), elevated GSM in 6/9 (median GSM 6.83 ng/ml) and elevated PAP in 5/9 patients (median PAP 4.02 ng/ml).

The mean marker levels in the remaining 26 patients without progression during follow-up were approximately equal to the initial measurements

Table 2 Follow-up Data in 35 Patients with Stable Disease at the Start of the Assays

		GSM		PSA		PAP	
		No. of patients	No. of patients (%) (> 4 ng/ml)	Mean (ng/ml)	No. of patients (%) (> 4 ng/ml)	Mean (ng/ml)	No. of patients (%) (> 2.2 ng/ml)
Stable disease after 12 months	26	3 (11.5)	1.30	7 (26)	3.60	4 (15)	1.01
Progression within 12 months	9	6 (66)	6.83	8 (88)	20.02	5 (55)	4.02

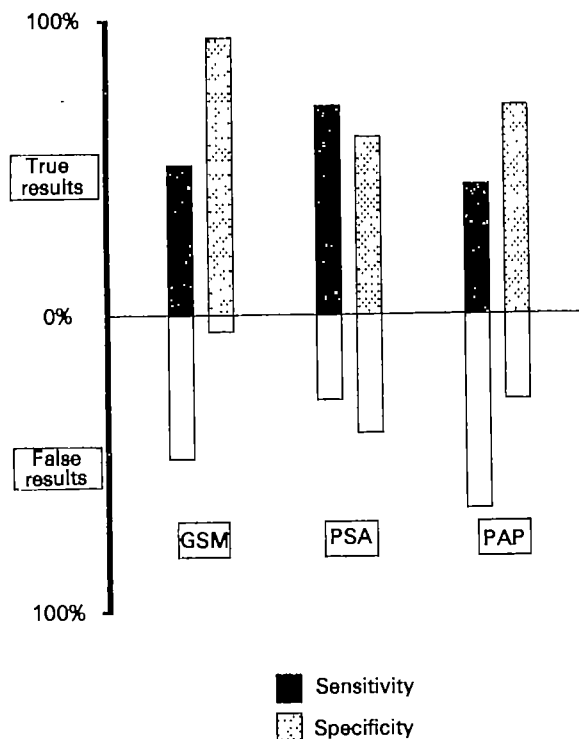


Fig. 2 True and false results with regard to specificity and sensitivity in patients with benign hyperplasia and newly detected prostatic cancer respectively.

(PSA 3.60, GSM 1.30, PAP 1.01 ng/ml), but raised levels of PSA were observed in 7 patients (26%), PAP in 4 (15%) and GSM in 3 (11.5%).

Discussion

Comparison of these 3 tumour markers has produced interesting results. The highest specificity was attained by GSM (94%) and the highest sensitivity by PSA (71%).

Using both PAP and PSA as a screening test, we found at least 1 tumour marker with an abnormal level in 31/41 patients (76%). By including GSM, the sensitivity increased to 85%; 5/6 patients within the normal range for all markers had an incidental carcinoma.

The definition of sensitivity in treated patients is of little value because therapy influences tumour growth as well as the production of tumour markers. More information on the efficiency of a marker is given by the detection of tumour progression. At the time of marker determination, 27/121 patients under therapy showed clinical progression. Using

all markers, progression was serologically detectable in 22 cases (81%). In the latter group, 18 patients had increased PSA and/or PAP levels; in the remaining 4 patients, only GSM was positive. In the stable disease group (94 patients), elevated levels of PSA were found in 39%, PAP in 12% and GSM in 10.6%.

The prognostic importance of these values in stable disease has yet to be determined. In 35 patients, PSA increased in 8/9 cases (88%), whereas GSM was raised in only 6/9 patients (66%) before clinical manifestation of progression. On the other hand, we found 7/26 patients (26%) with elevated PSA but without progression. It was concluded that PSA, used alone, tends to be less specific than GSM as a diagnostic tool for monitoring disease. A net gain in efficiency was obtained when using the 3 markers simultaneously. The highest risk of progression was observed in patients with an early increase in both PSA and GSM. PSA may be of most value in early warning of progression, but we suggest that GSM, because of the fewer number of false positive values, should also be used to provide additional information.

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Low Dose Methotrexate and Doxorubicin in Hormone-resistant Prostatic Cancer

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Summary—A group of 24 patients, all of whom had progressive disease following initial hormone therapy for advanced prostatic carcinoma, were given intravenous methotrexate (30 mg/m²) and doxorubicin (15 mg/m²) at 2-week intervals for a planned 6-treatment course. Seventeen patients completed the full course. Assessment included "quality of life" criteria, using the subjective assessment of performance status, severity of pain and analgesic consumption. Over half of the patients improved in each of these modalities and 8 (33%) improved in all 3. As toxicity was acceptable, low dose chemotherapy may have a part to play in these patients who present a difficult management problem.

The management of advanced prostatic carcinoma which has not responded to simple hormonal manipulation, or has relapsed after androgen deprivation, continues to be a therapeutic challenge. The treatment most commonly used is palliative radiotherapy to localised painful bony metastases. Half-body irradiation and strontium 89 are now being considered as useful further therapies in selected individuals. Systemic chemotherapy has had only limited success, partly because the population involved is elderly (with potential toxicity high) and partly because only a few drugs have even modest efficacy (Catalona, 1984). In addition, response is difficult to measure with any precision in the majority of patients. For some with relapsing disease it may be appropriate to offer palliative treatment with increasing doses of analgesia, but for others who might otherwise be quite active, it is reasonable to offer an alternative.

Responses have been claimed for 2 chemotherapeutic agents, doxorubicin and cisplatin, but toxicity would seem to preclude their use in most patients. A modified schedule of low dose doxorubicin given weekly has been shown to be well tolerated with good subjective responses. Torti *et*

al. (1983) used 20 mg/m² intravenously at weekly intervals in 25 patients. The majority reported an improvement in their pain, although it is conceded that this could have been a placebo effect. Four patients clearly had an objective partial response. Overall toxicity in the group was minimal. A similar experience was reported by the Yorkshire Urological Oncology Group using 10 mg/m² doxorubicin weekly (Robinson *et al.*, 1983). No objective response was obtained.

A comparative study by the National Prostatic Cancer Project (NPCP) in 1983 assessed the effect of methotrexate, cisplatin and estramustine phosphate in hormone-resistant prostatic cancer patients (Loening *et al.*, 1983). Methotrexate 60 mg/m² weekly gave the highest response rate (41%), using NPCP criteria which include patients with stable disease. Toxicity, mainly mucositis, was evident at this dose, but despite this, methotrexate was chosen by the NPCP as their new reference agent for further studies.

Since lower doses of methotrexate should be less toxic, a combination of methotrexate and doxorubicin given every 2 weeks might be better tolerated. Toxicity should be reduced and less frequent hospital visits are an advantage in elderly patients. We report the results of a study to assess the toxicity

and the response rate of these 2 agents in patients with hormone-resistant advanced prostatic carcinoma.

Patients and Methods

All patients had histologically proven prostatic carcinoma with confirmed metastases and objective evidence of progression of disease following standard hormone therapy. Progression was defined as the appearance of new bony lesions on a bone scan or X-rays or an increase in prostatic acid phosphatase on 2 occasions, within 3 months of each other, to more than twice the upper limit of normal. Patients had either relapsed after, or failed to respond to, prior hormonal treatment (orchiectomy and/or oestrogen treatment or antiandrogens). Prior radiotherapy to the prostate or to other lesions was permitted only if there was clear evidence of progression more than 3 months after the end of the course of radiotherapy.

There was no upper age limit. Patients were eligible for treatment if their performance status was <2 (Table 1), life expectancy was at least 3 months, pre-treatment haemoglobin was 10 g/dl or greater, the white cell count $4.0 \times 10^9/l$ or more, bilirubin 20 $\mu\text{mol/l}$ or less and creatinine 150 $\mu\text{mol/l}$ or less. Patients with other primary malignancies, those with cardiac disease requiring treatment with beta-blockers and those who were geographically inaccessible were excluded.

Ethical Committee approval was obtained by each participating clinician to enter patients into the study.

At entry a full history was taken, clinical examination carried out, weight and height measured, performance status noted, analgesic requirement recorded and pain assessment documented, the latter 3 on a 5-point scale (Table 1). A full blood count, urea, creatinine, electrolytes, prostatic acid phosphatase, liver function tests, alkaline phosphatase and plasma testosterone were assayed. The chest was X-rayed as well as metastatic bony lesions and, where applicable, a bone scan or liver scan was carried out. Prostatic size was assessed by digital examination.

Doxorubicin 15 mg/m² and methotrexate 30 mg/m² were given by intravenous injection into a fast running infusion. Folinic acid 15 mg *qid* orally was prescribed for 3 days, starting 24 h after chemotherapy had been administered. The same regimen was repeated every 2 weeks (subject to dose modifications if there was evidence of a rising

Table 1 "Quality of Life" Assessment

Performance status	Severity of pain	Analgesic consumption
0 Normal activity	None	Analgesics not required
1 Symptoms but ambulatory	Slight	Non-narcotic analgesics occasionally required
2 In bed 50% of time	Moderate	Non-narcotic analgesics regularly required
3 In bed 50% of time	Severe	Oral or parenteral narcotic analgesics occasionally required
4 100% bed-ridden	Intractable	Oral or parenteral narcotic analgesics regularly required

creatinine or decreased white cell or platelet count) for 6 courses. Reassessment of the radiological, biochemical and clinical findings was carried out 2 weeks after the sixth course. It was open to the clinician to continue the treatment every month thereafter up to a total dose of 500 mg/m² of doxorubicin.

Monitoring was carried out by a full blood count, urea, creatinine and electrolyte assay prior to each planned course, liver function tests monthly and weight, performance, status, analgesic requirement and pain assessments monthly. After the sixth course, X-rays of metastases and bone scans were repeated with measurement of any palpable lesions. Modification of the methotrexate regimen if severe mucositis occurred were included in the protocol but were not required as no patient developed this complication.

Response was based on the assessment criteria recommended by the British Prostate Group (Chisholm, 1980), *i.e.* complete objective regression, partial objective regression, stable response, objective progression and subjective response.

Results

Twenty-four patients were registered. The mean age was 70 years (range 55–85). Eleven patients had had previous radiotherapy for bony metastases prior to chemotherapy, and all had evidence of progressive disease. Seven patients failed to complete 6 courses of chemotherapy, 4 because of rapid deterioration with early death and 1 because of local progression leading to impaired renal function and a decision to withhold further treatment. Another patient developed persistent vomiting and

was withdrawn from the study after 3 courses. The seventh patient developed severe leucopenia with a white cell count dropping from $5.5 \times 10^9/l$ to $0.9 \times 10^9/l$ within 2 weeks of the first course of chemotherapy, and dying shortly thereafter. This patient was found to have almost total bone marrow destruction on a bone marrow scan (Haddock *et al.*, 1989), the result of which was not known until after treatment had been started.

Apart from these 2 major toxic problems, 2 patients developed mild alopecia and mucositis, 1 mild mucositis alone, 1 mild alopecia and 2 complained of malaise, although to what extent this was a feature of their disease or chemotherapy is debatable. At some time during the 6 courses, 8 patients reported some nausea when specifically questioned, even if very slight, but in none other than the one reported above was this sustained. In general the treatment was well tolerated. None of the patients who completed 6 courses showed any evidence of severe myelosuppression as assessed by the white cell (mean nadir $5.1 \times 10^9/l$; range $3.2-9.5 \times 10^9/l$) and platelet counts (mean nadir $204 \times 10^9/l$; range $70-323 \times 10^9/l$); 22 patients have died. The average survival from initiation of chemotherapy was 27 weeks (range 2-67). The 2 survivors are at 67 and 33 weeks respectively, but both have shown progression of disease. The longer survivor had 5 further courses of chemotherapy and subsequent palliative radiotherapy.

In no patient was there evidence of objective regression, either complete or partial. At assessment 2 weeks after the sixth course of chemotherapy or earlier withdrawal or death, 6 patients had stable disease and 18 objective progression. Subjective response was based on the triad of performance status, analgesic consumption and pain assessment. Twelve patients were considered "better", 2 showed "no difference" and 10 were "worse". The response in each group is shown in Table 2. In 8 patients there was improvement in all 3 modalities.

Table 2 "Quality of Life" Responses

	Performance status	Severity of pain	Analgesic consumption
Improved	12	13	12
Unchanged	5	4	5
Deteriorated	7	7	7

All three modalities improved in 8 patients

There was no coherent pattern in the biochemical or the haematological profiles of any of the response groups, although the trend for those who became worse clinically was for a rise in the acid and alkaline phosphatase and a gradual decrease in haemoglobin.

Discussion

This study has shown how difficult it is to assess the response to treatment in patients with a near terminal condition, who are elderly, where specific criteria are limited and where the quality of life produced by the treatment may be as important as objective improvement. It was not expected that low dose chemotherapy would produce objective regression, and so it proved. Just under one-third of the patients failed to complete the 6 courses; only 2 died or were withdrawn directly due to effects of chemotherapy and in others withdrawal probably reflected the advanced stage of disease.

One-third of the patients had improvement in all 3 modalities which were subjectively assessed, *i.e.* analgesic consumption, severity of pain and performance status, and overall felt better. Unfortunately, there was no information which could be used to predict whether a given individual was likely to benefit from such a regimen of low-dose chemotherapy.

Our results are less optimistic than those reported by Torti *et al.* (1983), but nevertheless some of our patients did benefit subjectively. This would support further studies of low dose chemotherapy in selected patients with advanced hormone-resistant prostatic carcinoma.

Acknowledgements

We are grateful to other members of the Scottish Urological Oncology Group who entered patients into the study: Messrs K. Baxby, M. Hehir, A. Rogers, D. A. Tolley and J. P. A. Weaver.

Co-ordination of the trial was carried out by staff of the Scottish Cancer Trials Office (Medical Research Council).

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Radical Nerve-sparing Prostatectomy with Epidural Anaesthesia in 100 Patients

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Summary—From August 1985 to January 1989, 100 patients were treated with radical nerve-sparing prostatectomy with epidural anaesthesia. Transrectal ultrasound evaluation was available for most of these patients. Using the anatomical techniques of early dorsal vein ligation, hypogastric artery control and epidural anaesthesia, blood loss was minimised and 55 patients required no transfusions. In addition, with the use of ultrasound, PSA determination and pelvic CAT scan, 73 of these 100 patients had organ-confined disease; 66 patients were potent pre-operatively and 42 are potent post-operatively.

A prospective study was made of 100 patients treated at a single institution by the same surgical team with radical nerve-sparing prostatectomy under epidural anaesthesia. All patients were followed up for at least 12 months (range 5–36). Pre-operative evaluation in patients with apparently localised disease included bone scan, pelvic CAT scan, PSA, acid phosphatase and transrectal ultrasound of the prostate. Since 1985, radical retropubic prostatectomy of the nerve-sparing variety has been performed at this institution according to the techniques described by Walsh *et al.* (1983). These techniques give priority to preservation of the nerves responsible for potency and preservation of bladder neck function. Attempts are also made to decrease haemorrhage secondary to early isolation of the hypogastric artery with early control of the dorsal vein complex. This report analyses the clinical and pathological staging, ultrasound and pathological staging, blood loss, and the time to restoration of erectile function in the 66 patients who were potent pre-operatively, 42 of whom remained potent post-operatively. In addition, 73% of patients undergoing these procedures had organ-confined disease as judged by clinical and pathological staging. This correlates well with other reports.

Patients and Methods

Nerve-sparing radical prostatectomy was carried out in 100 patients aged between 49 and 74 years, with a mean follow-up of 12 months. Standard clinical evaluation included physical and digital rectal examination, acid phosphatase determination, prostate specific antigen, bone scan, pelvic CAT scan, MRI in selected patients, and transrectal ultrasound of the prostate. Epidural anaesthesia was used in all cases.

Results

Pathology

Of the 100 patients, 73 received accurate clinical staging as compared to pathological staging. The latter revealed A2 disease in 9 patients, B1 disease in 41, B2 disease in 23 and microscopic Stage C disease in 27. Ultrasound staged patients correctly compared with the pathological staging in 73%. Ultrasound understaged 30% of patients and overstaged 8%. In 4 additional patients positive pelvic lymph nodes were found during pelvic lymph node dissection and they were excluded from the series. Acid phosphatase was elevated in 8% of patients pre-operatively. Prostate specific antigen was elevated in 50% pre-operatively and returned to normal within 16 days post-operatively; 42% of patients

had normal pre-operative and post-operative PSA values and 8% had an elevated pre-operative PSA that did not become normal post-operatively. These patients had the most extensive local disease in the seminal vesicle; they were treated with orchiectomy and the PSAs are now normal.

Blood replacement

A total of 61 patients undergoing radical nerve-sparing prostatectomy under epidural anaesthesia with early ligation of the dorsal vein complex and early control of the hypogastric vessels did not require blood transfusion and their average blood loss was 630 ml. Of the remaining 39 patients, 24 received a single autologous unit of blood, donated beforehand; 11 received 2 units of blood and 4 received 3 units. It is our policy for patients to donate at least 1 or 2 autologous units pre-operatively; these are stored in the blood bank for use should the need arise.

Erectile function

Of the 100 patients who underwent this procedure, 66 were potent pre-operatively and 42 were potent post-operatively. In the latter group, 14 had potency restored within 4 months of surgery, 12 regained potency within 10 months and in the remaining 16 patients potency was sufficient for vaginal penetration (5 at 11 months, 6 at 12 months, 3 at 13 and 2 at 14 months). Of the 24 patients who are impotent post-operatively, 4 have been followed up for less than 10 months but in 10 others more than 20 months have elapsed. The pathological stage of their disease had a direct influence on potency. Of 24 patients who were potent pre-operatively and impotent post-operatively, 14 were pathological Stage C, 6 were B2 and 4 were B1. In patients with B2 disease it has been our policy to preserve the neurovascular bundle unilaterally. In patients with small (<1.5) B1 nodules, both bundles are preserved. However, with larger B1 tumours only the contralateral neurovascular bundle is preserved. In spite of this, 13 of the 42 patients who were potent post-operatively had B2 disease. It is also interesting that none of the patients who were in their 50s, and who were potent prior to surgery, were impotent after surgery. This includes 3 patients with Stage C disease and 10 with B2 disease.

Bladder outlet complications

With regard to the bladder outlet, we use a technique to mucosalise the bladder as described by Walsh and Donker (1982): 4/0 chromic sutures are used to advance mucosa from inside the bladder to the

seromuscular surface outside, so making a "stoma" of the bladder. This allows for easy anastomosis to the urethral remnant. As a result of using this technique, only 6 patients have developed bladder neck contracture. In 4 cases this responded well to urethral dilatation and in the other 2 a TUR incision of the bladder was necessary. The incontinence rate was only 1%, with this patient incontinent 3 months post-operatively. The patients experience stress incontinence for approximately 6 to 12 weeks post-operatively and wear pads during that time.

Ultrasound

Transrectal ultrasound, using both the axial and the sagittal probe, was performed with the Bruel and Kjaer Ultrasound Machine. This unit has a 7 MHz probe and permits visualisation of both anechoic and hypoechoic areas, with good definition of the seminal vesicles. It is useful in assessing seminal vesicle disease and perhaps even more useful in allowing one accurate assessment by needle biopsy of areas that are questionable in terms of localised disease. Ultrasound enabled us to exclude from radical prostatectomy several patients who had microscopic seminal vesicle involvement as well as distal urethral sphincter involvement. Patients with seminal vesicle involvement are treated with external beam radiation at this institution. A final judgment on ultrasound is not possible until more prospective studies have been carried out.

Discussion

During the last 5 years, several advances have enabled urologists to stage localised prostatic carcinoma more accurately and to treat it surgically. The main goals of this new surgical technique have been to improve the continence rates and preserve potency. In addition to the anatomical contributions and advances of Walsh *et al.* (1983), blood loss can be minimised if close attention is paid to the dorsal vein complex, isolation of the cavernosal nerves and early control of the hypogastric vessels.

The use of transrectal ultrasound has also led to accurate assessment of localised disease. Lee *et al.* (1987) used this technique successfully to assess and biopsy any areas of a suspicious nature.

Controversy surrounds radical nerve-sparing prostatectomy and the question of "limiting the resection" and preserving the nerves responsible for potency. These questions have been addressed by Catalona and Dresner (1985). They compared

52 patients who underwent a nerve-sparing radical prostatectomy for clinically staged A or B disease with 25 patients treated by standard radical prostatectomy. Their results suggest that nerve-sparing radical prostatectomy can preserve sexual function in the majority of patients without compromising the adequacy of the resection. In the present series, patients with clinical B2 disease (or any induration of B1 disease extending into the area of the capsule) underwent unilateral excision of the involved neurovascular bundle. In addition, when the 100 patients undergoing this technique are compared with 30 patients treated prior to 1985, no increase is found in the number of patients with positive surgical margins. In fact, more patients treated with the nerve-sparing radical prostatectomy had organ-confined disease than the 30 patients treated with radical prostatectomy between 1980 and 1985.

Prostate specific antigen has been useful in our patients and early results indicate that it is an excellent marker for residual or progressive disease. In this small series, the results parallel those of Stamey *et al.* (1987) for the stage of disease. Epidural anaesthesia has helped to reduce the amount of blood replacement necessary. Comparison of patients in the present series with a similar group treated with radical prostatectomy under general anaesthesia reveals a difference in the number of patients requiring blood transfusion. Only 39 of our patients required transfusion during the intra-operative or peri-operative period and 55 patients required no transfusion. In a similar group of 30 patients treated under general anaesthesia, the average blood transfusion was 2.7 units. Theoretically, the lack of positive ventilation pressure may decrease the blood flow in the pelvic venous system, thereby reducing overall blood loss. It should be noted, however, that in this earlier series early dorsal vein ligation was not routinely practised.

In conclusion, it is possible to perform radical nerve-sparing prostatectomy in a safe and effective manner with minimal need for blood transfusion, providing attention is paid to anatomical techniques as outlined above. Bladder neck complications can be minimised if there is a relatively dry field, good exposure and mucosalisation of the bladder neck. An incontinence rate of 1% and a bladder neck contracture rate of 6% were obtained in this series. We believe that these factors have made radical prostatectomy a viable choice for many patients with localised prostatic carcinoma and it compares favourably with other treatments for this condition.

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Unilateral Testicular Torsion: Abnormal Histological Findings in the Contralateral Testis—Cause or Effect?

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Summary—A histological review of testicular biopsies of the contralateral testis, obtained at the time of surgical intervention for testicular torsion, was performed in 20 post-pubertal men.

Contralateral histological abnormalities were found in 12 specimens. The duration of torsion correlated well with the viability of the involved testis but not with the presence of contralateral abnormalities.

The high incidence of contralateral histological abnormalities and their nature suggest that they existed prior to the torsion since they would be unlikely to appear at such an early stage. We believe that some patients who suffer testicular torsion probably have congenital anomalies of both testes. These abnormalities involve testicular parenchyma as well as the suspension system.

Reduced fertility and abnormal semen analyses have been reported in patients following treatment for unilateral testicular torsion (Krarup, 1978; Bartsch *et al.*, 1980; Thomas *et al.*, 1984). Considerable debate exists as to the aetiology of these changes. Some authors suggest it is secondary to an effect exerted by the twisted testis on its contralateral mate (Bartsch *et al.*, 1980; Nagler and De Vere-White, 1982; Nagler *et al.*, 1984) while others believe it to be a pre-existing problem (Horica *et al.*, 1982; Thomas *et al.*, 1984; Hadziselimovic *et al.*, 1986).

For several years it has been our practice to obtain contralateral testicular biopsies at the time of detorsion or orchiectomy and contralateral orchiopexy. We now report the results of a histological review of the contralateral testicular biopsy in 20 post-pubertal men obtained at the time of surgical treatment of the torsion.

Patients and Methods

Records for the years 1980 to 1985 were reviewed and all cases of testicular torsion were identified.

Accepted for publication 3 August 1989

All post-pubertal patients who had contralateral testicular biopsies submitted in Bouin's solution have been included in this report. The records of these patients were reviewed in order to determine demographic parameters as well as operative information regarding duration of torsion and type of operation performed.

The pathology slides for each patient were coded and sent to The Armed Forces Institute of Pathology (AFIP), Washington, DC, where they were reviewed by 2 independent pathologists unaware of our institutional pathologist's interpretation of the slides. The only clinical information available to the AFIP pathologists was the patient's age, the operation performed and the duration of torsion. The reviewing pathologists were asked to comment specifically and in detail on the spermatogenesis of the contralateral testis in addition to the architectural findings.

Results

Twenty post-pubertal patients were included in this review. Their ages ranged from 13 to 31 years (mean 18 ± 1.2). The presumed duration of torsion

prior to treatment ranged from 8 to 672 h (mean 127 ± 40).

Contralateral histological abnormalities were found in 12 of 20 specimens (60%). These abnormalities included maturation arrest (5), germ cell degeneration (5), tubular hyalinisation (4), immature tubules (1) and focal thickening of the basement membrane (1) (Figs 1–4). Some specimens exhibited more than 1 abnormality (Table 1).

The treatment rendered and duration of torsion

are summarised in Table 2. Ten patients underwent orchiectomy of the involved testis with simultaneous contralateral orchiopexy. Eight of these patients had torsion for more than 24 h and 2 for less than 24 h. The other 10 patients underwent detorsion and bilateral orchiopexy; 5 of these patients had torsion for more than 24 h and 5 for less than 24 h.

Table 3 summarises the contralateral histology as a function of the surgical treatment. Five of the 10 patients who underwent orchiectomy had abnor-

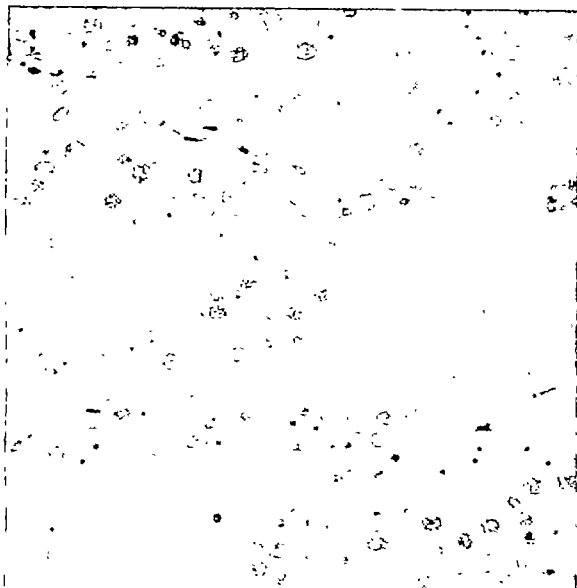


Fig. 1 Incomplete maturation arrest. (H and E $\times 160$).

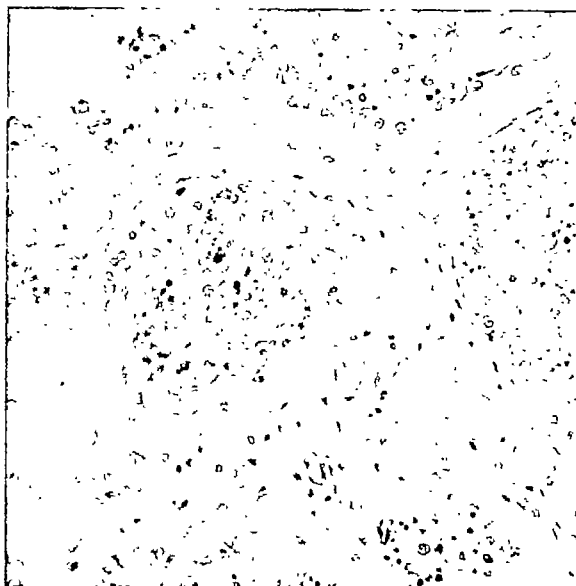


Fig. 2 Focal tubular hyalinisation. (H and E $\times 100$).

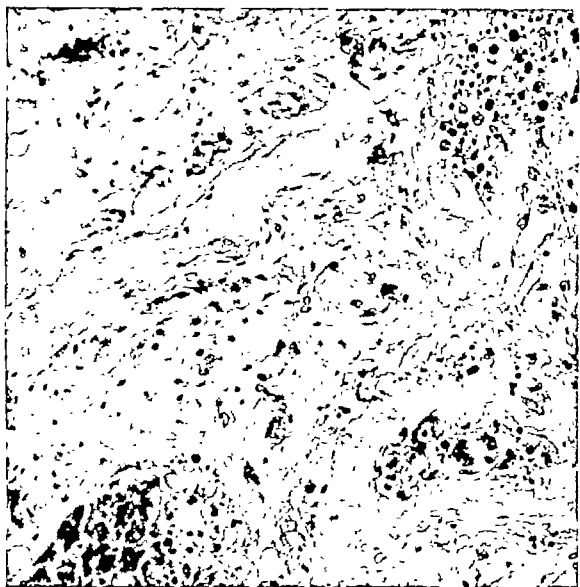


Fig. 3 Diffuse tubular hyalinisation. (H and E $\times 100$).

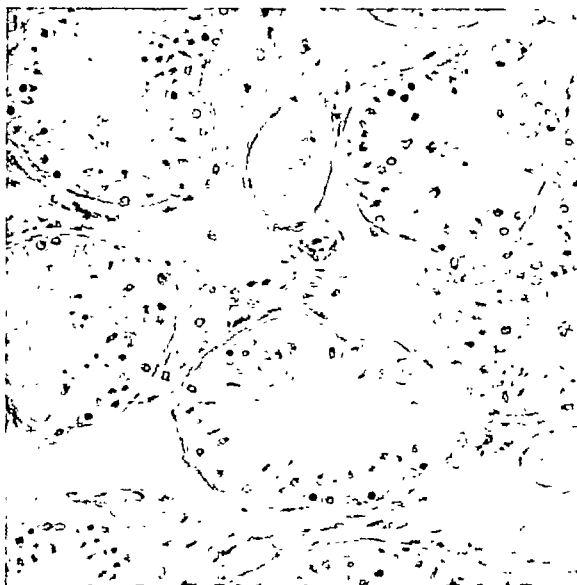


Fig. 4 Germ cell degeneration. (H and E $\times 100$).

mal contralateral histology, whereas 70% (7/10) of the patients treated by orchiopexy had abnormal contralateral histology.

The relationship between duration of torsion and contralateral histology is shown in Table 4. Contralateral abnormalities were found in 6 of the 13 patients with torsion for more than 24 h and in 6 of the 7 patients (85%) with torsion for less than 24 h.

Discussion

The pathogenesis of contralateral abnormalities in patients with unilateral testicular torsion is unclear. Krarup (1978) showed that fertility in these patients was reduced. Bartsch *et al.* (1980) studied the effect of the duration of torsion on fertility and showed that 43% of patients with torsion lasting less than 4 h had pathological or doubtful semen analyses at follow-up examination.

In an effort to clarify the aetiological factors involved, Nagler and DeVere-White (1982) designed an experimental animal model which seemed to indicate that the causative mechanism was immunologically mediated and that the damage to the contralateral testis was proportional to the duration of torsion. They suggested that the salvaged testis may represent a liability to the patient's contralateral testis and ultimate fertility. They also suggested that in post-pubertal animals, orchiectomy may be appropriate, even in the

absence of frank necrosis, in order to minimise the "immunologic threat" to the contralateral testis (Nagler *et al.*, 1984).

Our data indicate a correlation between the duration of torsion and testicular salvageability. Patients treated with orchiectomy had a much longer average duration of torsion than those treated with detorsion and orchiopexy. In this regard, our data resemble other data indicating that the longer the duration of torsion the more likely it is that the patient will require orchiectomy (Krarup, 1978; Bartsch *et al.*, 1980; Thomas and Williamson, 1983).

Regardless of the treatment used, 60% of our patients had contralateral testicular abnormalities on histological examination. These abnormalities were of a nature not commonly associated with acute events.

When contralateral histology was analysed with respect to temporal factors, it became apparent that the existence of contralateral abnormalities was not related to the duration of torsion or to the method of treatment (Tables 3 and 4). In fact, in our patients, contralateral histological abnormalities were associated with a shorter duration of torsion than in those patients with normal contralateral histology (Tables 3 and 4).

The observation of a high incidence of contralateral histological abnormalities, independent of the duration of torsion, as well as the nature of these

Table 1 Demographic Distribution, Surgical Intervention and Contralateral Histology

Patient	Duration	Age (years)	Treatment	Contralateral histology
T.L.	8 h	23	Orchiopexy	Hypospermatogenesis, focal tubular hyalinisation
H.G.	9 h	18	Orchiectomy	Active spermatogenesis
G.P.	12 h	18	Orchiopexy	Active spermatogenesis, focal tubular hyalinisation
J.B.	14 h	17	Orchiopexy	Active spermatogenesis, focal tubular hyalinisation
A.L.	14 h	14	Orchiopexy	Active spermatogenesis, focal germ cell loss
M.E.	18 h	17	Orchiectomy	Active spermatogenesis, focal germ cell loss
E.M.	18 h	14	Orchiopexy	Active spermatogenesis, focal thickening of basement membrane
R.N.	48 h	26	Orchiopexy	Active spermatogenesis
F.R.	48 h	14	Orchiectomy	Active spermatogenesis, focal areas of complete maturation arrest, focal hyalinisation of tubules
J.T.	48 h	14	Orchiectomy	Focal germ cell loss, incomplete maturation arrest
D.T.	48 h	15	Orchiopexy	Active spermatogenesis, immature tubules
E.H.	72 h	14	Orchiectomy	Extensive germ cell loss
D.R.	72 h	17	Orchiectomy	Focal germ cell loss, incomplete maturation arrest
V.L.	5 days	21	Orchiectomy	Active spermatogenesis
J.M.	7 days	30	Orchiopexy	Active spermatogenesis
R.H.	10 days	13	Orchiopexy	Active spermatogenesis
M.R.	10 days	14	Orchiectomy	Active spermatogenesis
R.B.	14 days	17	Orchiectomy	Active spermatogenesis
G.S.	14 days	14	Orchiopexy	Active spermatogenesis, incomplete maturation arrest
B.H.	28 days	31	Orchiectomy	Active spermatogenesis

Table 2 Treatment and Duration of Torsion

Treatment	Duration of torsion (h)		Total
	< 24	> 24	
Orchiectomy	2	8	10
Orchiopexy	5	5	10
Total	7	13	20

Table 3 Treatment and Contralateral Histology (Mean duration of torsion in h)

Treatment	Contralateral histology		Total
	Normal	Abnormal	
Orchiectomy	5 (275)	5 (52)	10 (164)
Orchiopexy	3 (152)	7 (64)	10 (91)
Total	8 (229)	12 (59)	20 (127)

Table 4 Duration of Torsion and Contralateral Histology (Mean duration of torsion in h)

Duration of torsion (h)	Contralateral histology		Total
	Normal	Abnormal	
< 24	1 (9)	6 (14)	7 (13)
≥ 24	7 (261)	6 (104)	13 (188)
Total	8 (229)	12 (59)	20 (127)

histological changes, suggest that these abnormalities pre-existed the torsion. These findings lead us to believe that patients who suffer testicular torsion often have congenital anomalies of both testes. These abnormalities probably involve testicular parenchyma as well as the suspension system and may be responsible for the reduced fertility potential reported in these patients.

We therefore believe that the twisted testis probably has a minimal, if any, effect on the

contralateral testis and that treatment should be determined only by its viability.

Acknowledgement

We acknowledge Ms. Dorothy Divilly Jennings' invaluable assistance in bringing this manuscript to print.

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Necrotising Soft Tissue Infections of the Perineum and Genitalia

Bacteriology, Treatment and Risk Assessment

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Summary—Necrotising soft tissue infections of the perineum and genitalia are associated with a high rate of mortality and morbidity. We reviewed the records of 29 consecutive patients to investigate the possible correlation between clinical outcome and number of types of bacteria cultured, focus of infection, presence of diabetes, patient age, renal function and delay until presentation. The patients had an average of 3.9 bacterial organisms cultured intra-operatively (range 1–9). Patients with a rectal focus of infection had a greater number of bacteria and required longer hospitalisation and more operative procedures than patients with dermal or urethral foci. Those over the age of 60 had significantly longer hospital stays and higher mortality. Diabetes and impaired renal function did not increase mortality or morbidity. Suprapubic cystostomy was required in 24 patients (83%), diverting colostomy in 9 (31%) and orchiectomy in 3 (10%). Six patients (21%) died despite broad spectrum antibiotics and aggressive and frequent surgical debridement.

An abrupt, rapidly progressive, gangrenous infection of the genitalia was originally described by Fournier in 1883. Since that time about 500 similar cases have been reported (Biswas *et al.*, 1979; Jones *et al.*, 1979; Lamb and Juler, 1983; Carroll *et al.*, 1986). Although many different classifications have been proposed (Meleney, 1933; Rudolph *et al.*, 1975; Bubrick and Hitchcock, 1979; Kaiser and Cerra, 1981), this process probably represents a spectrum of disease best characterised as a fulminant soft tissue infection that may spread along subcutaneous planes and result in necrosis of the skin, fascia or subcutaneous tissue. Although Fournier's original case was idiopathic, now the origin of these infections can be traced to the rectum, the genitourinary tract or the skin (Gray, 1960; Flanigan *et al.*, 1978; Lamb and Juler, 1983; Carroll *et al.*, 1986). Their seriousness is reflected in the high morbidity and mortality rates (21%).

To predict the clinical outcome of these infections, we undertook a risk assessment. We correlated focus of infection, presence of diabetes, age, number of bacterial species cultured per patient, renal function and delay until presentation with outcome as measured by duration of hospitalisation, number of surgical procedures, complications and mortality. The bacteriology of these unusual infections was reviewed along with the acute surgical management and early reconstructive procedures.

Patients and Methods

Between 1975 and 1988, 29 patients (28 male and 1 female) aged 14 to 81 years (average 54) were treated at the hospitals of the University of California, San Francisco, and at San Francisco General Hospital for necrotising soft tissue infections of the perineum and genitalia. Patient records were reviewed for clinical history, physical examination, laboratory data, intra-operative Gram

staining and culture testing, predisposing diseases, number and type of operation, duration of hospitalisation, complications and survival. Student's *t*-test and the χ^2 test were used for statistical analysis.

Results

Clinical presentation varied among patients (Table 1). The time from onset of local symptoms until medical attention was sought averaged 5 days (range 1–30). The source of infection could be traced to the rectum (N=14), the urethra (N=6) or the skin (N=9). Of the 6 patients with urethral foci, 4 had indwelling Foley catheters and 2 had documented urethral strictures. The diagnosis of a dermal source was based on a history of trauma or local infection (folliculitis or balanitis) in patients with normal results on cystourethroscopy and rectal examination under anaesthesia. Associated conditions included alcohol abuse in 15 (52%) and diabetes in 12 (41%).

Leukocytosis with left shift was present in 27 patients (93%). Eight patients (28%) presented with true hyponatraemia (Na < 131 mEq/l); 4 others had pseudohyponatraemia secondary to hyperglycaemia. Eleven patients presented with a serum creatinine > 2.0 mg/dl.

Table 2 shows the most common bacteria cultured. In Table 3 these results are grouped according to aetiological foci. Infection tended to be polymicrobial, with an average of 3.9 cultured organisms per patient (range 1–9). Both aerobic and anaerobic bacteria were found in 20 (69%). Aerobic bacteria alone were cultured in 7 patients (24%); an anaerobic bacterium alone was found in 1 (3%).

In the Figure the percentage of patients with aerobic Gram-positive, aerobic Gram-negative, anaerobic Gram-positive, anaerobic Gram-negative and *Corynebacterium* is correlated with the aetiological source. The combination of the anaerobes *Bacteroides* species and *Peptostreptococcus*

with the aerobic *Escherichia coli* was found in 8 patients (28%), all with a perirectal source of infection.

Necrotic tissue was debrided promptly in all patients. Within 24 h the wound was examined and debrided further as required (average number of procedures 4.2 [range 1–11]). Suprapubic cystostomy drainage, diverting colostomy and orchiectomy were performed as necessary. After arrest of infection, 21 patients underwent surgical reconstruction (Table 4). Ten required immediate thigh pouches for testicular protection until subsequent definitive reconstruction; 7 patients required hyperalimentation.

Six patients died (21%). Other complications are presented in Table 5. The average hospital stay for surviving patients was 37 days (range 11–126). Clinical follow-up averaged 22 months (range 3 months–6 years). Follow-up surgery included 6 colostomy take-downs and 2 revisions of reconstructed surgical wounds.

Length of hospital stay, mortality, complications, number of bacteria cultured at initial debridement and number of operative procedures were correlated with aetiological focus, diabetic risk factor, age over 60, 5 or more bacterial species cultured at initial debridement, creatinine above 2.0 mg/dl and delay until presentation (Table 6). Patients with a rectal focus had longer hospital stays (48 days, $P < 0.05$), required more operative procedures (average 5.4, $P < 0.05$) and had more bacterial species cultured per infection (average 4.5, $P < 0.05$) than those patients with dermal or urethral aetiological foci. Patients with diabetes did not suffer more complications or require more surgical procedures or a longer hospital stay. Patients older than 60 years had longer hospital stays (42 days, $P < 0.05$) and greater mortality (N=5, $P < 0.05$). Five or more bacterial species cultured at initial debridement as well as renal impairment at presentation did not increase hospital stay, mortality, complications or number of operative procedures. Patients

Table 1 Clinical Presentation in 29 Patients

Signs and symptoms	No. of patients (%)
Pain	29 (100)
Swelling	29 (100)
Fever	19 (66)
Crepitus	18 (62)
Skin necrosis	10 (34)
Shock	4 (18)
Altered mental status	3 (14)

Table 2 Most Common Bacteria Cultured

Bacteria	No. of patients (%)
<i>Streptococci</i> (all species)	20 (69)
<i>Bacteroides</i> (all species)	19 (66)
<i>Escherichia coli</i>	16 (55)
<i>Peptostreptococcus</i> (all species)	14 (48)
<i>Corynebacterium</i>	9 (31)
<i>Staphylococcus</i> (all species)	7 (24)
<i>Klebsiella pneumoniae</i>	5 (17)
<i>Proteus</i> (<i>Morganella</i>) species	4 (14)

Table 3 Results of Intra-operative Bacteriology in Culture Testing

	Aetiological Focus			Total* patients
	Rectum	Skin	Urethra	
<i>Streptococci</i>				
Group A		3		3
Group B		1	1	2
Group C	1			1
Group D (enterococcus)	4		2	6
Group G	1	1	1	3
Non-groupable <i>Strep. viridans</i>	3	1	1	4
Total <i>Streptococci</i>	9	6	5	20
<i>Staphylococcus</i>				
<i>Aureus</i>			1	1
<i>Epidermidis</i>	3	2	1	6
Enteric Gram-Negative				
<i>Escherichia coli</i>	12	3	1	16
<i>Klebsiella pneumoniae</i>	3	1	1	4
<i>Pseudomonas aeruginosa</i>	1			1
<i>Proteus (Morganella)</i>	3		1	4
<i>Corynebacteria</i>				
<i>Corynebacterium vaginalis</i>	1		2	3
<i>Corynebacterium</i> (not speciated)	3	2	1	6
Anaerobic Bacteria				
(Gram-positive)				
<i>Clostridium</i> (not perfringens)	1			1
<i>Peptostreptococcus</i> species	11	3		14
(Gram-negative)				
<i>Bacteroides</i> (all species)	16	2	1	19
<i>Fusobacterium</i>	1			1

*Some patients had more than 1 focus of infection.

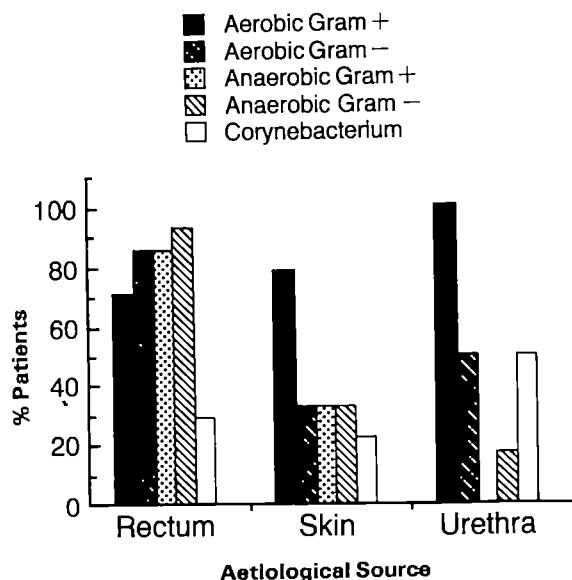


Fig. Correlation between type of bacterium and focus of infection in 29 patients.

delaying presentation beyond 5 days required more operative procedures (3.9, $P < 0.05$).

Discussion

Necrotising soft tissue infections of the perineum and genitalia should not be considered idiopathic (Carroll *et al.*, 1986). Virtually all patients have an identifiable focus of infection, with the rectum being the most common. The process spreads by penetrating the genitourinary diaphragm and interstices in Colles' fascia to extend to the genitalia (Gray, 1960).

The predisposition of patients with diabetes is well documented but poorly understood. Influential factors include small vessel disease predisposing to ischaemia, defective phagocytosis hindering defence mechanisms, and increased urinary tract infection secondary to functional urinary tract obstruction from diabetic neuropathy (Thornton, 1971). However, in the 12 patients with diabetes in the present series (41%), their disease bore no correlation with a poorer outcome.

Table 4 Acute Surgical Management and Early Methods of Reconstruction

	No. of patients (%)
Acute operations	
Debridement	29 (100)
Suprapubic cystostomy	24 (83)
Diverting colostomy	9 (31)
Orchiectomy	3 (10)
Reconstructive methods*	
Split-thickness skin graft	14 (67)
Delayed closure	11 (52)
Thigh pouches	10 (48)
Skin flaps	6 (29)

* Some patients underwent more than 1 method of reconstruction.

Table 5 Deaths and Complications in 29 Patients with Necrotising Soft Tissue Infection of the Perineum and Genitalia

Complication	No. of patients (%)
Death	6 (21)
Cardiovascular collapse (pressor agent)	7 (24)
Respiratory failure (intubation)	5 (17)
Renal failure (requiring dialysis)	3 (10)
Coagulopathy	2 (7)
Urethral stricture	2 (7)
Acalculous cholecystitis	1 (3)
Cerebral vascular accident	1 (3)
Chordee	1 (3)
Fistula	1 (3)
Infertility	1 (3)

Some patients had more than 1 complication.

The observation of multiple bacterial organisms cultured from each patient suggests the probable importance of bacterial synergy in the development of these infections (Stone and Martin, 1972). Another feature of synergistic necrotising infec-

tions is gas in the soft tissue or crepitus on physical examination. Although this classically has been associated with clostridial anaerobic myonecrosis (Finegold, 1982), non-clostridial bacterial causes of crepitant infections have been reported (Weinstein and Barza, 1973), including those cultured in our series: *Escherichia coli*, *Klebsiella*, *Peptostreptococcus*, *Bacteroides*, *Fusobacterium* and (rarely) *Streptococcus pyogenes*. In fact, *Clostridium* was cultured in only 1 of our patients and was notably of the non-perfringens type (it is thought that 90% of pathogenic clostridial myonecrotic infections are due to the perfringens species [Finegold, 1982]). Of the 24 patients with Gram stains, none had the classic findings of Gram-positive large "boxcar" bacilli, suggesting that the absence of *Clostridia* did not result from faulty anaerobic culture techniques.

In 5 of the patients with a urethral focus of infection and 3 with dermal foci, *Streptococcus* was cultured alone or with either *Staphylococcus epidermidis* or *Corynebacterium*. Although each of these latter is considered normal skin flora, pathogenicity has been shown for both. Three patients had Group A *Streptococci*, 2 Group G and 2 Group B. It has previously been proposed that *Streptococcus* Group A can cause necrotising fasciitis by itself (Giuliano *et al.*, 1977; Hammar and Wanger, 1977) when combined with the risk factors of trauma and surgery. Our patients with *Streptococci* had either indwelling Foley catheters or injuries to the skin.

Of interest is the observation that 9 patients (31%) had *Corynebacteria* cultured from the intra-operative wound. Several *Corynebacterium* species form part of the normal flora of the human respiratory tract, other mucous membranes and skin (Washington, 1981). *Corynebacterium vaginalis* (now called *Gardnerella vaginalis*) is implicated in vaginitis (McCormack *et al.*, 1977) but not in necrotising infections; other *Corynebacteria* parti-

Table 6 Correlation of Aetiological Focus and Diabetic Risk Factor with Mortality, Number of Surgical Procedures, Complications and Length of Hospital Stay

Risk factor	No.	Hospital stay (days)	Mortality (%)	Complications (%)	Bacteria	Procedures
Rectal focus	14	48*	23	38	4.5*	5.4*
Dermal focus	9	31	11	33	2.6	3.2
Urethral focus	6	30	33	83	3.3	3.5
Diabetes	12	28	33	58	3.2	3.4
Age ≥ 60	13	42*	38*	31	2.8	3.6
Bacteria ≥ 5	7	26	27	43	—	4.2
Creatinine ≥ 2 mg/dl	11	35	27	55	3.5	3.2
Delay ≥ 6 days	11	34	9	36	3.7	3.9*

* $P < 0.05$.

cipate in the pathogenesis of acne (Rosenberg, 1969) and *Corynebacterium diphtheriae* produces a powerful exotoxin that causes diphtheria in humans. Whether the *Corynebacteria* cultured in this series played a role in the pathogenesis of these patients' necrotising soft tissue infections is unclear.

The mechanism of bacterial pathogenicity is diverse. The invasiveness of *Bacteroides* species is catalysed by the production of enzymes that cause tissue damage, including collagenase, hyaluronidase and DNase (Finegold, 1982). *Bacteroides* also produce a heparinase that may account for the observed vascular thrombosis. *Clostridium* species depend on a different mechanism producing various exotoxins that can cause massive tissue necrosis in a short period of time (Weinstein and Barza, 1973).

The pathogenicity of *Streptococci* and *Staphylococci* species depends on the elaboration of extracellular products. Group A *Streptococcus* is known to make streptokinase (Fibrinolysin), which transforms plasminogen to plasmin—an active proteolytic enzyme that digests fibrin and other cellular proteins. Another enzyme, streptodornase, depolymerises DNA. Because purulent exudates owe their viscosity largely to deoxyribonucleoproteins, streptodornase, by liquefying them, may thus promote infection. Both *Streptococci* and *Staphylococci* produce hyaluronidase, which splits hyaluronic acid, an important component of connective tissue. *Staphylococci* also produce coagulase, an enzyme-like protein that clots oxalated or citrated plasma, generating clotting activities. The coagulase may deposit fibrin on the surface of the *Staphylococci*, possibly altering their ingestion by phagocytic cells or their destruction within such cells. Coagulase production is considered synonymous with invasive pathogenic potential (Duma *et al.*, 1969; Musher and McKenzie, 1977; Simon, 1986).

Most enteric Gram-negative bacteria (*Escherichia coli*, *Klebsiella*, *Proteus* [*Morganella*]) possess complex lipopolysaccharides in their cell wall. These substances, otherwise known as endotoxins, are liberated during infection and can cause an experimentally reproducible clinical response (Gram-negative sepsis) (Young *et al.*, 1977). Of the 7 patients with the complication of cardiovascular collapse, enteric Gram-negative organisms were cultured in 6.

The treatment of necrotising soft tissue infections begins with surgical debridement of all devitalised tissue immediately upon diagnosis. Re-exploration is usually necessary within 24 h to confirm arrest of the infection. In our series, suprapubic cystostomy was necessary in 24 patients (83%) either to divert

infected urine or to avoid urethral catheterisation. A diverting colostomy was required in 9 (31%) to keep the wound free from faecal soilage. Broad spectrum antibiotics directed at both aerobic and anaerobic bacteria should be initiated immediately, awaiting culture results. In most cases, our standard regimen is to start the patient on triple antibiotic coverage with ampicillin, gentamicin and metronidazole for Gram-positive, Gram-negative and anaerobic bacteria respectively. In recent years we have tailored therapy to include the newer cephalosporins (avoiding renal toxicity) pending intra-operative bacterial culture sensitivity testing. When choosing antibiotic therapy, it is important to remember that ischaemic and necrotic tissue will not benefit from even the most powerful antibiotic; hence the most important treatment remains immediate surgical debridement. We also recommend parenteral hyperalimentation in patients who are unable to meet their caloric needs by enteral feeding (*i.e.* those with endotracheal intubation, large wounds, pre-existing malnutrition).

Despite extensive infection and wide-spread debridement, early and satisfactory reconstruction is possible. The redundancy of the scrotal skin allows complete or partial coverage by delayed closure. Larger or residual defects can be managed with split-thickness skin grafts. Early in this series, 3 patients (all over age 65) underwent orchiectomy. As can best be determined from the operative reports, the testes were removed not because of ischaemia but because of extensive tissue damage in the surrounding scrotal, groin and perineal area, as well as the patients' ages and difficulty with dressing changes. Because of the independent testicular blood supply it would be unusual for the testis to be necrotic; indeed, we were unable to document this finding throughout this series of 29 patients. With improvement in reconstructive techniques, we have found orchiectomy to be essentially unnecessary. For testicular protection, thigh pouches can be used as interim or long-term coverage. We have also used skin flaps in our series in those patients in whom maintenance of fertility was a consideration.

In conclusion, necrotising fasciitis of the perineum and genitalia remains a serious disease. Despite aggressive treatment, mortality and morbidity remain high, especially among older patients and those with a rectal focus of infection. In this group, more bacterial organisms were cultured and they required more surgical procedures and longer hospitalisation than patients with a dermal or urethral aetiological focus or patients with diabetes.

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Tunica Vaginalis: an Aid in Hypospadias Surgery

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Summary—Despite the improvements that have been made in equipment and in the techniques of hypospadias repair, some patients still present with failed repairs and urethral fistulas. In such patients the lack of prepuce leads to difficulty in obtaining adequate tissue for further reconstruction.

In 14 patients with hypospadias who had already undergone surgery, a tube was formed from proximal penile or scrotal skin and wrapped by pedicled tunica vaginalis; 4 patients with urethral fistulas were treated in the same way after primary repair of the fistulas. Excellent cosmetic and functional results were achieved in all but 1 case. The technique is simple, has few complications and is recommended in the treatment of patients with failed hypospadias repair and urethral fistulas.

There are many methods of hypospadias repair but high success rates with the MAGPI procedure and the transverse island pedicle flap technique have revolutionised the treatment of hypospadias (Duckett, 1986). Despite these advances, 10 to 20% of patients develop urethral fistulas (Belman, 1985) and the lack of prepuce can lead to insufficient tissue being available for reconstruction. Snow (1986) described a method of wrapping tunica vaginalis around the neo-urethra and the author has used this technique in 14 patients with hypospadias and 4 patients with urethral fistulas.

Patients and Methods

Fourteen patients with failed hypospadias repairs and 4 with urethral fistulas were treated between November 1986 and November 1988. Their ages ranged from 4 to 22 years (mean 15). Nine patients had had 1 previous operation, 4 had undergone 2 procedures, 4 had had 3 procedures and 1 had had 4 previous operations for repair of hypospadias or fistulas. Eleven patients had penile hypospadias at presentation; in 2 cases the meatus was located at the penoscrotal junction and 1 patient had scrotal hypospadias. Two patients had a penile fistula and 2 had multiple fistulas at the penoscrotal junction.

Technique

A vertical incision is made on the ventral aspect of the penis, from the corona to the hypospadiac meatus; chordee, if present, is corrected by excising all fibrous tissue until an artificial erection demonstrates a straight penis. Depending on the level of the meatus, proximal penile or scrotal skin is incised to form a tube and freed from the underlying tissue. The tube is created by continuous 5/0 catgut sutures. The end of the tube is sutured to the skin at coronal level. One of the testes is then brought to the wound and scrotal attachments dissected free from the tunica vaginalis. A transverse incision is made at the tunica vaginalis close to the epididymis at the lower pole of the testis and a pedicled rectangular flap is formed (Fig. 1). This flap is carried over the tube, covering the ventral aspect of the penis from the corona to the pedicle of tunica vaginalis. The flap is sutured to the penis with fine 6/0 catgut as laterally as the incision permits, but not extending to the dorsal side. This forms a tube wrapped by a layer of pedicled tunica vaginalis (Fig. 2). A polyethylene tube is placed in the neo-urethra as a stent and left in place for 3 to 5 days; a suprapubic tube diverts the urine for 7 to 10 days.

In patients with a urethral fistula, the tract is excised and the fistula closed with 6/0 catgut sutures. The tunica vaginalis is wrapped over the

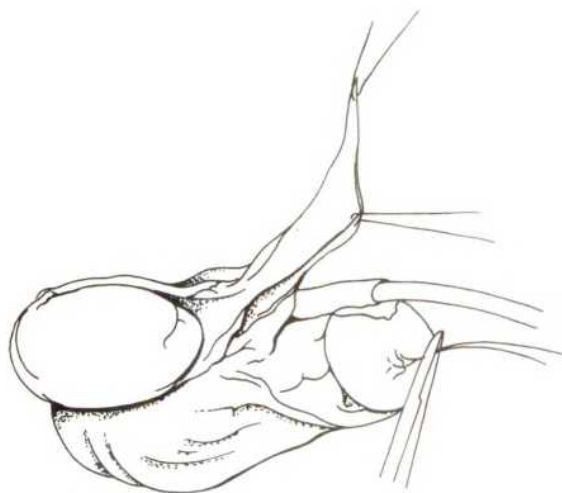
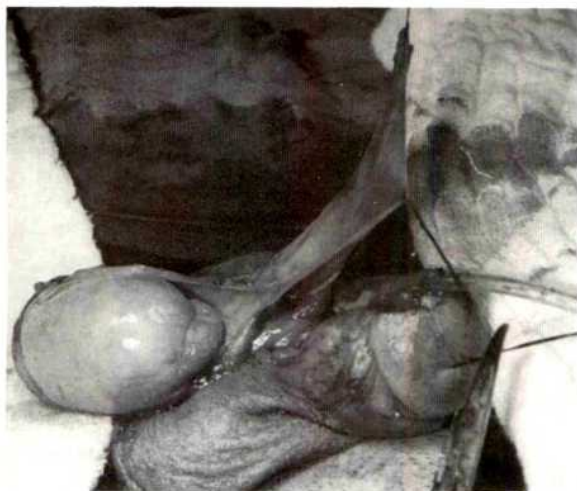


Fig. 1 A rectangular pedicled flap of tunica vaginalis is formed from the right testis.

ventral aspect of the penis to cover the area of repair as described above. A polyethylene tube is left in the urethra for 2 to 5 days.

Results

Of 14 patients with failed hypospadias repairs, excellent cosmetic and functional results were obtained in 13. They all had a good projectile stream of urine from the new meatus. In 1 patient, a 24-year-old man in whom 4 unsuccessful attempts had been made to correct his penile hypospadias, the technique was unsuccessful. He developed a severe wound infection and the entire tube sloughed despite high doses of systemic antibiotics.

The urethral fistulas of 4 patients were closed

satisfactorily. In 2 patients with hypospadias and 1 with penoscrotal multiple fistulas, pus was present in the urethral meatus after the second post-operative day; only 1 developed a wound infection with dehiscence. All 3 patients made a good recovery following aspiration of the stent and appropriate antibiotic treatment. There were no complications related to the use of tunica vaginalis.

Discussion

Although recent advances in hypospadias surgery have revolutionised reconstructive procedures, a small number of patients with failed repairs and urethral fistulas remain a problem for the urologist. MAGPI and transverse island pedicle flap tech-

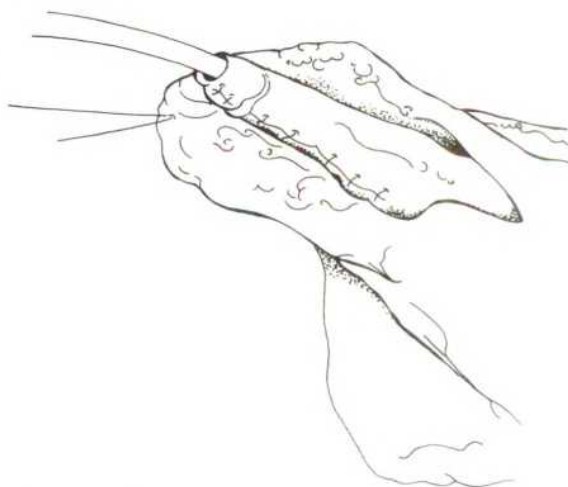
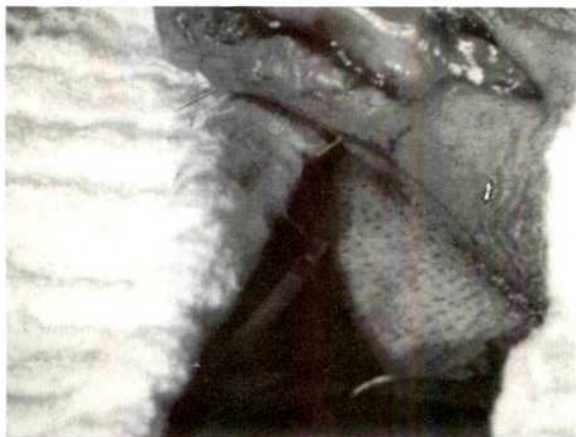


Fig. 2 Tunica vaginalis is sutured to the ventral aspect of the penis to wrap the tube.

niques are highly successful in correcting this deformity (Duckett, 1986). Improvements in suture materials, antiseptic solutions, dressings, more powerful antibiotics and delicate handling of tissue have all contributed to these favourable results. The problem cases, however, are those patients with a lack of prepuce and excessive fibrous tissue following previous operations.

Tunica vaginalis has been used to reconstruct the urethra with some success (Ariyoshi, 1967). Snow (1968) used tunica vaginalis to wrap the neo-urethra at the time of hypospadias repair and reported satisfactory results in 20 such patients and in 2 with urethral fistulas.

The technique described here is simple and applicable to all age groups. No foreign tissue or material is involved and the use of tunica vaginalis presents no risk to the patient. Snow (1986) showed that this pedicled tunica vaginalis retained its vascularity and did not interfere with the vascularity of the underlying tube. One of his patients had a small scrotal haematoma but there were no testicular complications in the present series. The importance of avoiding damage to the dorsal neurovascular bundle was emphasised by Snow (1986), but with the present technique, which involves wrapping the ventral aspect only of the penis, such damage is not possible. Meticulous dissection is employed to avoid damaging the spermatic vessels, vas deferens, epididymis or testis.

The aesthetic appearance of the testis after the operation is satisfactory. When properly dissected, a generous length of tunica vaginalis is obtained and there is no traction on the testis. A slightly high

testis soon after the operation settles back to normal within 6 months.

The presence of infection in 3 patients, in whom pus drained via the urethra (not from the wound), suggests that the tunica vaginalis may be a barrier to infection. These results indicate that pedicled tunica vaginalis can be used effectively in patients with failed hypospadias surgery and urethral fistulas, and its use probably reduces the complications of such repairs.

Acknowledgements

I am grateful to the urologists at Gülhane Military Academy and Faculty of Medicine, Ankara, who allowed me to use this technique on their patients. I also thank Mr R. H. Whitaker, Consultant Urologist at Addenbrooke's Hospital, Cambridge, for his advice and critical review of the manuscript.

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Penile Prostheses in the Management of Impotence in Sickle Cell Disease

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Summary—Priapism lasting more than 24 h in adults with homozygous sickle cell disease usually results in impotence. The dense fibrosis of the corpora cavernosa which destroys the normal vascular erectile system of the penis also complicates insertion of penile prostheses. Our experience in 5 patients is reviewed. Sharp dissection and dilatation were necessary to form a tunnel for the prosthesis, which was more easily excavated anteriorly and posteriorly through a dorsal incision than for the length of the corpora through a traditional perineal-scrotal incision. Damage to the tunica was common and subsequent migration of the prosthesis necessitated an additional 11 procedures under general anaesthesia. Despite these technical difficulties, the procedure allowed satisfactory intercourse. The average interval between onset of impotence and implantation was 4 years. Early implantation before the dense fibrosis develops might give more satisfactory results.

Priapism in sickle cell disease presents 2 different clinical patterns, stuttering and major attacks (Emond *et al.*, 1980). Short stuttering attacks are generally nocturnal, recurrent, last 2–6 h, are relieved by simple measures and do not appear to affect subsequent sexual function. Major attacks last more than 24 h and their outcome is determined by the age of the patient, attacks after the age of 15 years being generally followed by complete impotence. The mechanism of impotence is the dense fibrosis of the corpora cavernosa which replaces the normal delicate frond-like vascular spaces, destroying the vascular erectile system. Sensation and ejaculation are normal and failure of sexual intercourse is mechanical due to lack of rigidity of the shaft of the penis. Penile prostheses are commonly used in the treatment of impotence in other conditions but only 1 report of this procedure in sickle cell disease was found on review of the literature (Pryor, 1981). Since the pathology of impotence in sickle cell disease might be expected to complicate insertion of such prostheses, experience with this procedure in 5 patients is reviewed.

Patients and Methods

The patients attended the sickle cell clinic at the University Hospital of the West Indies. All had homozygous sickle cell disease confirmed by haemoglobin electrophoresis under alkali and acid conditions, and compatible HbA₂ and HbF levels. They were selected from a group of impotent patients in whom at least 18 months had elapsed since the major attack of priapism; there was no evidence of recovery of function. All had surgical procedures performed under general anaesthesia without pre-operative transfusion.

The technique of implantation of the prosthesis (Douglas, 1987) entailed a combination of sharp dissection and dilatation to create a channel for its insertion. The Small-Carrion semi-rigid prosthesis (Small *et al.*, 1975) was used initially in all patients, although the dense fibrosis of the crura did not allow the crural tips to be inserted; these were trimmed and the end placed under the pubic symphysis. In early procedures, midline scrotal-perineal incisions were used. Because of difficulty in fashioning a tunnel through the length of the corpora, this approach was later abandoned in

favour of dorsal incisions and excavation of the corpora anteriorly and posteriorly prior to insertion of the prosthesis.

Case Reports

Case 1. M.C. At age 20 years he first attended the sickle cell clinic with a 12-month history of stuttering priapism. A major attack of priapism for 2 days at age 26 years was treated by cannulation and irrigation of the corpora under general anaesthesia. Complete impotence followed and 4 years later, a Small-Carrion prosthesis was inserted through a perineal-scrotal incision. The prosthesis functioned well and the patient had a child 8 years after operation. In the same year the right prosthesis migrated anteriorly and extruded painlessly through the glans penis and was removed by the patient. Reasonable sexual function continues with the remaining left prosthesis.

Case 2. C.P. At age 21, and without preceding stuttering priapism, a major attack of priapism occurred and resolved spontaneously after 4 days. Complete impotence followed and 3 years later a Small-Carrion prosthesis was inserted through a perineal-scrotal incision. While fashioning a tunnel, the dilator burst the left corpus into the urethra, necessitating a urethral repair. Fibrous tissue in the right corpus was excised to allow insertion of the prosthesis. Four days later the right prosthesis ulcerated through the glans penis and was removed under general anaesthesia. Over the next 3½ years, 4 further procedures were performed under general anaesthesia to reposition the left prosthesis, which migrated anteriorly under the glans, then laterally through the tunica, then dorsally, appearing below the skin at the coronal sulcus. When both prostheses appeared subcutaneously on the left side, removal and subsequent reimplantation were necessary. Following the last procedure, 7 years ago, there has been reasonable function and the birth of a child.

Case 3. H.S. At age 24, and without preceding stuttering priapism, he developed a major attack of priapism for 1 week which resolved after aspiration and irrigation of the corpora with heparinised saline. Complete impotence followed and 3 years later a Small-Carrion prosthesis was inserted through a perineal-scrotal incision after sharp dissection and dilatation. Following the procedure, the left prosthesis was noted to be just under skin proximal to the glans; the incision was reopened and the prosthesis repositioned. Three months later the left prosthesis again projected subcutaneously below the glans; it was removed and reinserted in a new tunnel under general anaesthesia. The prosthesis functioned reasonably for 2 years, but the patient then developed severe motor neurone disease which inhibited further attempts at intercourse.

Case 4. H.P. At age 24 he attended the sickle cell clinic with stuttering priapism twice monthly which increased

to 3 to 4 times weekly by age 34. At age 37 a major attack of priapism lasting 10 days resolved slowly with conservative therapy. Complete impotence followed and 10 years later a Small-Carrion prosthesis was inserted through a dorsal midline incision with dilatation of the corpora anteriorly and posteriorly. At follow-up the left prosthesis was well placed but the right was close to the skin. Function has been adequate, although the patient is troubled by premature ejaculation.

Case 5. P.B. At age 20, stuttering attacks of priapism occurred and at age 21 he had a major attack for 5 days relieved by a cavernosal-spongiosal shunt performed under general anaesthesia. One month later, pain at the base of the penis and a haemorrhagic discharge from the incision in the glans were attributed to infection and possible sloughing of the septum secondary to prolonged cavernosal ischaemia. Complete impotence followed and 1½ years later an attempt was made to insert a Small-Carrion prosthesis through a dorsal incision. This failed because the prosthesis travelled anteriorly through the cavernosal-spongiosal shunt which was still patent. Three months later the shunt was closed under general anaesthesia and 1 year after the initial insertion of the prosthesis a Pearman prosthesis was inserted through a dorsal incision. After 1 month this had eroded through the urethra and was removed. One year after this a Pearman prosthesis was again inserted through a dorsal incision with difficulty because of the fibrosis. Four years later the prosthesis is lying under the skin distally and the patient is scheduled for a further repositioning procedure.

Discussion

From these 5 case reports it is clear that considerable technical difficulty attends the implantation of even simple prostheses in the fibrotic corpora of impotent patients with sickle cell disease. Tunnels had to be cut by sharp dissection and dilatation, and damage to the tunica allowed subsequent migration of the prosthesis. Satisfactory initial placement was difficult and even then, migration of the prosthesis was common. Insertion of the prosthesis by traditional methods through an incision in the perineal-scrotal area compounded these problems, since this required formation of a tunnel for the entire length of the corpora. Access to the mid-corpora through a dorsal incision with dissection anteriorly and posteriorly was technically easier and this was previously suggested by Harty and Amin (1981).

These 5 patients required a total of 15 surgical procedures under general anaesthesia with a mean duration of 1.6 h. Migration of the prostheses, requiring surgical correction 11 times, occurred through the urethra (2), through the glans penis (1), under the glans (2), laterally under the skin (5) and

at the coronal sulcus (1). Migration through the glans also occurred and was completed spontaneously in 1 patient. Despite these surgical difficulties, no patient regretted the decision for implant surgery and all have had satisfactory intercourse, although there was disappointment at the size of the implanted organ and at pain associated with displacement of the prosthesis.

Since such technical difficulties attend the insertion of a simple, semi-rigid prosthesis of the Small-Carrion or Pearman type, there appear to be very limited opportunities for the more sophisticated inflatable prostheses currently available.

Dense fibrosis of the corpora is characteristic of post-priapism impotence from many causes (Herzberg *et al.*, 1981; Pryor, 1988; Winter and McDowell, 1988), although it is our impression that the fibrosis is more dense in patients with sickle cell disease. Following priapism in non-sickle cell conditions, it is customary to wait at least 1 year for any spontaneous return of potency. In sickle cell disease, spontaneous function almost never returns (Emond *et al.*, 1980), yet the fibrosis developing during this waiting period may compromise the success of subsequent implant surgery. In these 5 patients the mean interval between onset of impotence and implantation was 4 years. Since spontaneous return of erectile function following a major attack of priapism in sickle cell disease is extremely unusual, a trial of early implantation within 3 to 6 months of the major episode appears justified and may give better results.

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Out-patient Sclerotherapy of Idiopathic Left-sided Varicocele in Children and Adults

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Summary—Between 1983 and 1989, 334 patients with idiopathic left-sided varicocele were referred for transfemoral sclerotherapy; 323 were adults and 11 were children.

The standard site of injection of the sclerosing solution (Varicocid–Natriummorrhuat 55 mg, Benzylalkohol 20 mg) was the mid-portion of the spermatic vein. The upper third was injected only in cases where the catheter could not be negotiated further (*e.g.* abnormalities in the course of the spermatic vein or its drainage into the intrarenal veins). The amount of sclerosing material was predetermined fluoroscopically using contrast material. Occasionally, in cases of high catheter positioning, the Varicocid was injected fractionally. The amount injected was always between 1 and 3 ml. Of 80 patients studied 1 year later, varicoceles were still present in 3 (4%).

The best results were achieved in patients with small varicoceles (Grade I), normal testicular volume and normal FSH levels; 29% showed an improvement in sperm count and 27% an increase in sperm motility, while sperm morphology improved in only 7%. The conception rate was 11%.

In 1938, Fischer was the first to describe a non-operative trans-scrotal approach for the treatment of varicocele. Thereafter, percutaneous transfemoral sclerotherapy gained in popularity as an effective complication-free ambulatory procedure (Iaccarino, 1977; Lima *et al.*, 1978; Weissbach *et al.*, 1981; Zeitler *et al.*, 1980; Morag *et al.*, 1984; Thon *et al.*, 1986; Fobbe *et al.*, 1987; Halden and White, 1987; Sigmund *et al.*, 1987; Bach *et al.*, 1988; Pryor and Howards, 1988; Smith *et al.*, 1988).

Sclerotherapy of varicoceles is reported to be possible in 80% of cases, with the persistence rate ranging from 5 to 10% (Weissbach *et al.*, 1981; Thon *et al.*, 1986; Fobbe *et al.*, 1987; Sigmund *et al.*, 1987; Bach *et al.*, 1988).

Opinions differ as to the most effective site for the injection. Fobbe *et al.* (1987) recommended deep instillation of the sclerosing agent at the level of the inguinal ring. Others favour injection at the level of L3–4 (Zeitler *et al.*, 1980; Thon *et al.*, 1986). Catheter systems also differ: single lumen catheters and coaxial systems (Fobbe *et al.*, 1987) with 7 F

guiding balloon catheters, 2.5 F therapy catheters and guide wires are used.

We describe the techniques used and the results obtained in 334 patients.

Patients and Methods

Between October 1983 and March 1989, 334 patients with left-sided idiopathic varicoceles were referred for transfemoral sclerotherapy; 323 were adults between the ages of 18 and 39 years who had presented with testicular discomfort or subfertility. The remainder were children aged between 9 and 14 years with pronounced varicocele (Grades II or III). In 7 of these children the condition was discovered after their mothers noticed a painless swelling of the scrotum; 1 boy had a hypotrophic testis. The remaining 4 had complained of a painful scrotal swelling.

Most of the patients (90%) were referred from areas within a 130 km radius of this institute. The technique used was essentially that of Iaccarino (1977) and Lima *et al.* (1978) together with the developments of Zeitler *et al.* (1980). Under local

anaesthesia, using the Seldinger technique, an individually pre-shaped 7 F (occasionally 5 F) spermatic catheter was passed through the femoral vein into the left spermatic vein to the level of L3-4. Prior to this, the exact location of the point of entry of the spermatic vein was established by forcefully injecting the renal vein. If a competent venous valve was encountered which rendered phlebographic demonstration of the spermatic vein impossible, the catheter was repositioned into the intrarenal venous system. A non-ionic contrast material (Omnipaque/Iohexol, Ultravist/Iopromid, Schering AG, Berlin, FRG) was then injected. If reflux into a collateral vein was seen, an attempt was made to cannulate it (Fig. 1). If this was not possible, an attempt was made to push through the

competent valve in order to place the catheter at the appropriate (L3-4) position. In cases where the catheter reached only as far as L2-3 level, measured amounts of contrast material were injected in order to determine the volume of sclerosing material necessary to thrombose the vein without endangering the renal venous system through reflux. Thus sclerotherapy was still possible under these circumstances (Fig. 2).

If neither a 7 nor a 5 F catheter could be inserted far enough into the spermatic vein (vein too narrow, tortuosity, spasm), a 3 F catheter was introduced coaxially through the indwelling 7 F catheter (Angiomed, Karlsruhe, FRG). This often led to successful sclerotherapy.

Between 1 and 3 ml of Varicocid 5% in adults, 0.5 to 1 ml in children (Kreussler and Co. GmbH, Wiesbaden-Biebrich, FRG) were injected. This could also be instilled fractionally. The injection was carried out with the patient doing a Valsalva manoeuvre and in a 25 to 30° reverse Trendelenburg position. The air-block technique described by Sigmund *et al.* (1987) was also used. Ten minutes after sclerotherapy, contrast material was injected and, if necessary, a further 0.5 to 1 ml of Varicocid was instilled. After approximately 20 min, renal phlebography was repeated, especially in cases where intrarenal spermatic vein collaterals had been demonstrated.

In all 323 adults a pre-treatment semen analysis was performed twice, and in 287 (88.9%) this was done 3 times. At follow-up 1 year later (3 examinations were conducted in each patient with intervals of 3 months between them), 80 patients were seen again. The number of post-treatment semen analyses varied. The sperm counts of 49 patients (61%) were evaluated 3 times, those of 27 twice (34%) and in 4 men only 1 analysis (5%) was performed.

Semen was produced at the hospital following a 5-day period of sexual abstinence. The samples were analysed as soon as they had become liquefied. Sperm motility was investigated microscopically in the untreated samples after 30, 60, 120 and 240 min. The sperm counts were performed in a Thoma-Zeiss counting chamber. The liquefied ejaculate was diluted 1:20 with physiological saline and 1 drop of triphenyl tetrazolium chloride was added to the dilution to kill the spermatozoa. Sperm morphology was evaluated in stained smears.

Results

In 265 patients (79.3%), transfemoral sclerotherapy was carried out without difficulty; 43 patients

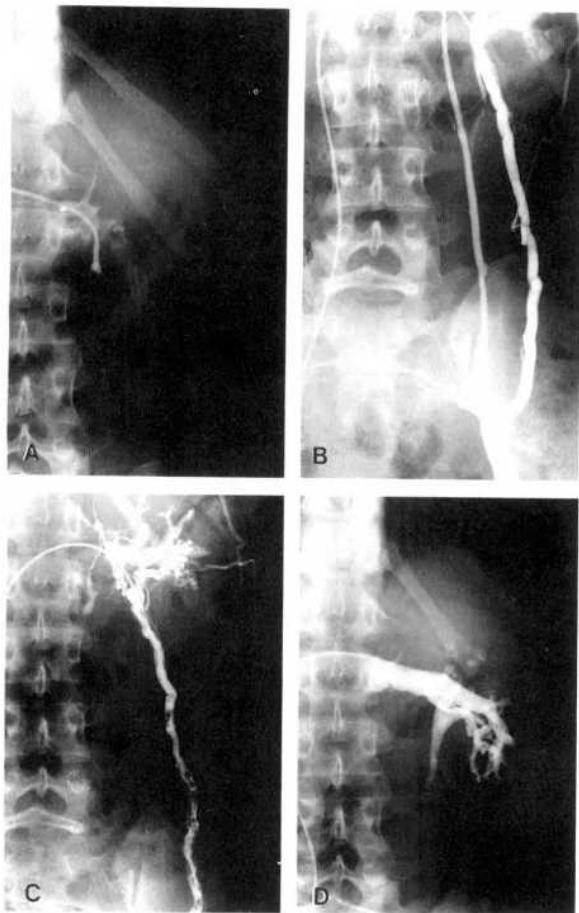


Fig. 1 (A) Competent valve of spermatic vein at a typical location. (B) Intrarenal orifice of a second spermatic vein and antegrade opacification of the typically positioned spermatic vein with contrast medium. (C) Condition following administration of Varicocid via the intrarenal spermatic vein and formation of thrombi. (D) Phlebography of intrarenal venous system by Valsalva's manoeuvre showed no reflux into the spermatic vein.

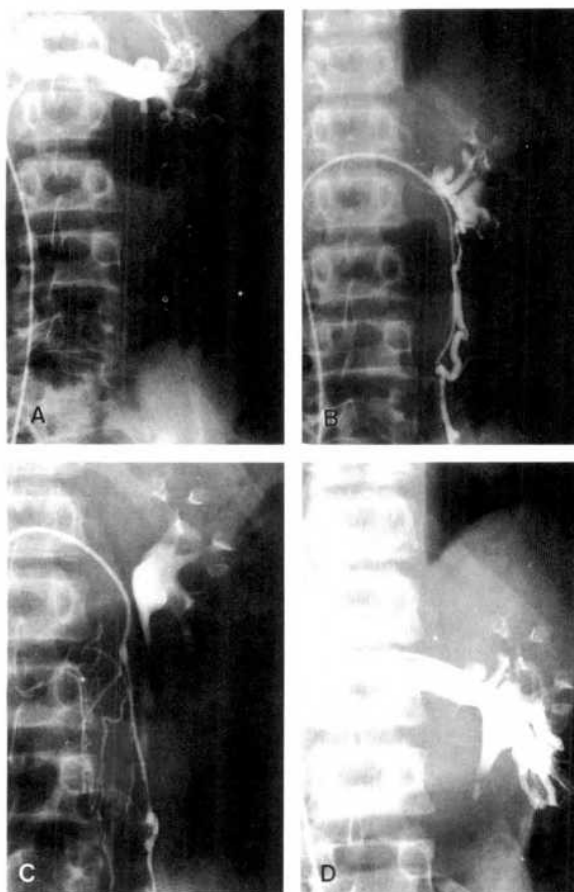


Fig. 2 (A) Competent valve in spermatic vein, second intrarenal point of entry. (B) Phlebogram of spermatic vein following perforation of competent valve. (C) Injection of contrast medium into spermatic vein following sclerotherapy and withdrawal of catheter; demonstration of thrombus formation and very fine, previously invisible collaterals. (D) Phlebography of renal vein by Valsalva's manoeuvre. Reflux into spermatic vein no longer detectable.

(12.9%) could not be treated by this method owing to atypical venous anastomoses. In 26 cases (7.8%) referred because of possible recurrence after varicocelectomy, phlebography demonstrated no evidence of a patent spermatic vein and sclerotherapy was not performed.

Of 135 patients who were asked to return for follow-up 1 year later, 80 complied and were evaluated (59.3%). Three (4%) had evidence of recurrent or persistent varicoceles. None of the children had a recurrence. An increase in sperm count was achieved in 29% of cases and increased sperm motility in 27%, while sperm morphology improved in only 7% (Table 1). Patients in group

IV, *i.e.* those with the most favourable pre-treatment findings (Table 2), showed a marked improvement in sperm count and motility. Age and duration of subfertility had no effect on improvement in the spermiogram (Table 3). Fertility, however, depended upon varicocele grade, pre-treatment testicular volume and FSH levels (Table 4). The sperm count improved in 16/23 men with Grade I varicoceles (70%) but remained unchanged in 26/46 patients with Grade II varicoceles (56%); in 9/11 men with Grade III varicoceles (82%) the sperm count was reduced after treatment (Table 3). The total sperm count also improved in 21/23 men

Table 1 Changes in Sperm Count, Motility and Morphology

	Sperm count		Sperm motility		Sperm morphology	
	No.	%	No.	%	No.	%
Improvement	23	28.8	22	27.5	6	7.5
No change	46	57.5	37	46.3	66	82.5
Deterioration	11	13.7	21	26.2	8	10.0
	80	100	80	100	80	100

Table 2 Changes in Sperm Count, Motility and Morphology Within and Between the Groups* (Before and After Scleropathy (n))

Group	Sperm count (mill/ml)		Sperm motility (%)		Sperm morphology (% of normal forms)	
	Before	After	Before	After	Before	After
I	16	7	28	18	3	2
II	39	32	24	22	5	5
III	20	18	18	19	18	10
IV	5	23	10	21	57	63

*Classification according to MacLeod (1969).

Table 3 Effects of Age, Duration of Subfertility and Grade of Varicocele on Sperm Count

Sperm count	Age (years)	Duration of subfertility (months)	Grade of varicocele		
			I	II	III
Improvement (n = 23)	20-39 (29.5)	7-88 (27.6)	16	6	1
No change (n = 46)	19-40 (31.2)	8-107 (28.4)	8	26	12
Deterioration (n = 11)	22-38 (32.1)	11-62 (29.2)	1	1	9

Table 4 Effects of Testicular Volume and Pre-treatment FSH Levels on Sperm Count

Sperm count	Left testicular volume		Pre-treatment FSH level	
	< 13 ml	> 13 ml	Elevated	Normal
Improvement (n = 23)	2	21	—	23
No change/deterioration (n = 57)	48	9	39	18

(91%) with normal testes (testicular volume > 13 ml), while the findings for 48/57 men with hypotrophic testes (84%) remained unchanged or deteriorated (Table 4). Only patients with normal FSH levels benefited from sclerotherapy (23/23). By contrast, 39/57 patients with elevated FSH levels (68%) showed no increase in total sperm count.

The rate of conception was 11% (9/80).

Complications

There was 1 instance of femoral artery puncture. The twelfth patient developed phlebitis of the pampiniform plexus, leading to swelling and erythema of the left scrotum. These were successfully treated with scrotal elevation and ice packs.

There were 3 cases of injury and perforation of the spermatic vein during insertion of the guide wire, and very few side effects from contrast material with the use of a non-ionic solution.

In 1 patient thought to have a recurrent varicocele, the flexible guide wire tip formed a hook-like configuration within the venous system. Pulling on the wire caused the patient some abdominal discomfort, but it was eventually removed without problems. Sclerotherapy was not felt to be necessary, since there was no retrograde filling of the pampiniform plexus seen at the time of phlebography.

Discussion

Only Fobbe *et al.* (1987) recommend injecting the sclerosing agent at the level of the inguinal ring. Others prefer the L3–4 level and most of our procedures were carried out at this level. If the sclerosing catheter was unable to reach the L3–4 level, the procedure was not terminated. Instead, small amounts of contrast were injected with the patient performing a Valsalva manoeuvre and we were thus able to determine the maximum amount

of contrast which could be safely accepted by the spermatic vein without reflux occurring into the renal venous system. The same volume of Varicocid was then used. If reflux occurred after application of a small amount of contrast medium (0.5 ml), an attempt was made to insert a 3 F catheter. This enabled us to perform a further 6 sclerotherapies.

The amount of sclerosant injected varied from 0.5 to 1 ml in children and 1 to 3 ml in adults. The average dose was approximately 2 ml, and in cases showing collateral drainage into the intrarenal venous systems the fractionated method of injection was adopted. Figures 1C and D and 2C and D demonstrate thromboses successfully obtained by this technique. The instillation of sclerosing agent at the level of the inguinal ring is not recommended because of the risk of causing thromboses within the pampiniform plexus. Also, in the event of partial duplication of the spermatic vein with a reverse-Y configuration, it is possible that one branch might remain patent, resulting in persistence of the varicocele.

It is likely that all that has been reported with regard to sclerotherapy in the treatment of varicoceles also applies to the use of heated contrast material (Smith *et al.*, 1988), although there are few reports in the literature to date.

The use of spirals or balloons is less effective, since only the spermatic vein and not its collaterals is thrombosed (Weissbach *et al.*, 1981). Also, the placement of metal foreign bodies is not without potential problems. For example, one does not know what the long-term effects of such a spiral might be, and both the spiral and the balloon are prone to dislocation and migration.

Our results following percutaneous sclerotherapy in 79% of potential candidates are in agreement with those found in the literature. The fact that only 59% of patients reported for follow-up 12 months later is disappointing. The recurrence or persistence rate of 3.8% corresponds to reports in the literature (Thon *et al.*, 1986; Fobbe *et al.*, 1987; Halden and White, 1987; Sigmund *et al.*, 1987; Bach *et al.*, 1988). West German health insurance regulations do not provide for routine out-patient follow-up in clinics and we were therefore unable to re-examine our patients by Doppler sonography. However, it would appear from our results that sclerotherapy is not inferior to surgery. Since general anaesthesia is not required, the procedure can also be carried out without analgesia or sedation, despite the recommendation to the contrary by Halden and White (1987); no surgical dissection is involved and transfemoral sclerother-

apy on an out-patient basis seems to be the method of choice.

The reported rates of improvement in the spermogram and conception following surgery or sclerotherapy for varicocele are 27 to 84% and 24 to 53% respectively (Scott and Young, 1962; Macleod, 1969; Brown, 1976; Dubin and Amelar, 1977; Gall *et al.*, 1979; Marks *et al.*, 1986). However, these results should be interpreted with caution, since different methods of selection were used, the evaluation criteria were not always the same and the methods of follow-up were not comparable. As a result, it is not possible to compare the results of these studies. If the spermogram findings are used as the criterion for success, the pre- and post-treatment findings must be adequately classified. The classification described by MacLeod (1969) is the most suitable for this purpose. In our study group, sperm count and motility showed the clearest improvement in the patients with the best pre-treatment findings. There was a connection between grade of varicocele and testicular volume before treatment and the semen quality after treatment. This is consistent with the results of Okuyama *et al.* (1988). Of the 80 patients followed up, those who benefited most from sclerotherapy in terms of an increase in fertility were those with a small varicocele (Grade I), normal testicular volume and normal FSH concentrations.

Transfemoral sclerotherapy of idiopathic varicoceles is the method of choice in most European countries.

The site of injection of the sclerosing agent is usually the mid-portion of the spermatic vein (L3–4) and the maximum amount is 3 ml. If the catheter cannot be placed at that level, contrast can be injected to determine the amount of sclerosing agent that can safely be used. Fractional injections are appropriate in such situations.

Since improvements in sperm count and motility were found mainly in patients with small varicoceles, normal testicular volume and normal FSH levels, it is worth considering whether patients with large varicoceles (Grades II or III), markedly reduced testicular volume and elevated FSH values should be referred for treatment of varicocele only because of infertility.

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Case Reports

Neonatal Xanthogranulomatous Pyelonephritis

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Case Report

A male neonate aged 21 days presented with the clinical features of septicaemia. His birth weight (2575 g) had been appropriate for gestational age (36 weeks).

The salient clinical and laboratory findings were BP 150/90, acidosis, hyponatraemia (Na 113 meq/l) and hypercalcaemia (Ca 3.13 mmol/l). The serum creatinine concentration was 49 mmol/l. Blood cultures grew *Staph. epidermidis*, as did a suprapubic aspirate of urine.

Ultrasound examination demonstrated gross right hydronephro-nephrosis. Micturating cystourethrography excluded posterior urethral valves but showed grade V vesicoureteric reflux into an ectopic ureter arising from the bladder neck (Fig. 1). ^{99m}Tc DTPA scan revealed non-function of this renal unit. The left kidney functioned well.



Fig. 1 MCUG showing influx into a dilated ectopic ureter.

Following correction of the metabolic disturbance and control of sepsis, the infant underwent right nephroureterectomy. Recovery was complete.

The hydronephrotic kidney showed several yellow 2-mm nodules in the parenchyma. These were organised lipogranulomata, some centred around collecting ducts and others distorting renal parenchyma (Fig. 2). There was a diffuse, mainly acute pyelonephritis. These appearances indicated focal xanthogranulomatous pyelonephritis (stage III). There was also renal dysplasia with focal fetal cartilage.

Comment

Xanthogranulomatous pyelonephritis is rare in childhood. Two forms, focal and diffuse, have previously been reported from this centre (Bagley *et al.*, 1977). The protean manifestations of this condition have led to erroneous diagnoses of Wilms' tumour, tuberculosis, renal carcinoma and perinephric abscess. Treatment is by nephrectomy, although the bilateral form necessitates conservative resection (Kural *et al.*, 1987).

The precise aetiology remains unclear. Chronic urinary infection is regarded as an integral component of the disease process, with congenital tract anomalies a predisposing cause. In the present case the age (21 days) precluded chronic infection from being causative and indicted congenital dysfunction, obstructive or refluxing as the major factor. Indeed the displacement of the parenchyma by the

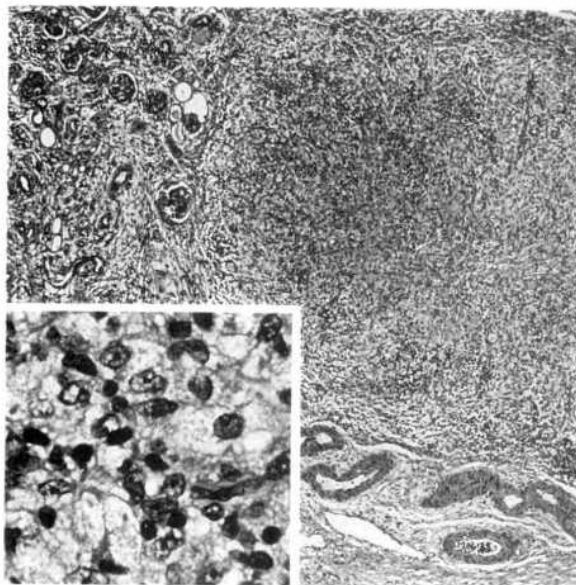


Fig. 2 Intermediate xanthogranuloma (stage III) displacing renal cortex (H and E $\times 63$). Inset: foamy lipophages (H and E $\times 630$).

xanthogranulomata (Fig. 2) and the stage III morphology (Møller and Kristensen, 1980) indicated long-standing disease and therefore a prenatal origin.

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Symptomatic Plasmacytoma (Myeloma) Involving the Bladder

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We report a unique case of plasmacytoma (myeloma) involving the bladder.

Case Report

A 75-year-old female presented with irritative bladder symptoms for 3 months; she had also noticed passing blood *per rectum*. Examination was normal except for 2 small anterior wall rectal polyps. The ESR was 44 but otherwise routine haematology and biochemistry were normal. There was significant pyuria and *Escherichia coli* bacteriuria. Intravenous urography showed a thick walled and scalloped bladder suggestive of either chronic pan cystitis or diffuse neoplastic infiltration (Fig. 1).

At cystoscopy the bladder was small, rigid and haemorrhagic and suspicious of carcinoma *in situ*; random biopsies were taken. One rectal polyp was excised but a second submucosal nodule was left *in situ*.

Histology of the rectal polyp and bladder biopsies revealed plasmacytoma with diffuse cell infiltration (Fig. 2) and monotypic immunohistochemical staining for lambda light chains only. The diagnosis of multiple myeloma was further confirmed by elevated serum

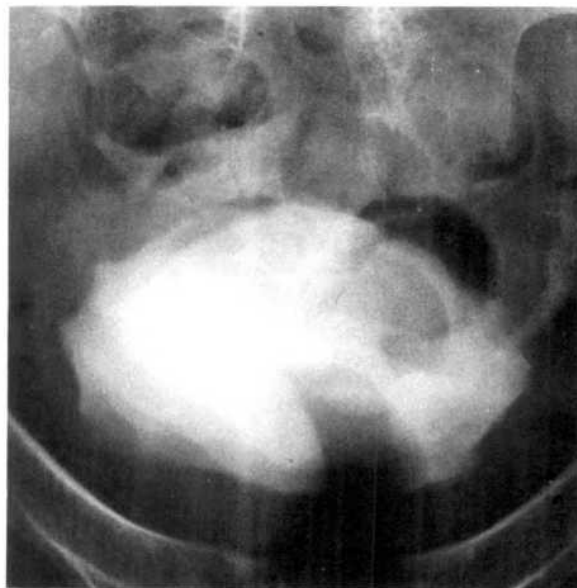


Fig. 1 Intravenous urogram showing thickened and scalloped bladder wall.

paraprotein (10 g/l) but skeletal survey, marrow aspirate/biopsy and urine Bence Jones testing were all unexpectedly normal.

Cyclical treatment ($\times 3$) with melphalan and prednisone achieved complete remission as shown by resolution of bladder symptoms, disappearance of the rectal nodule and normalisation of serum plasmaphoresis.

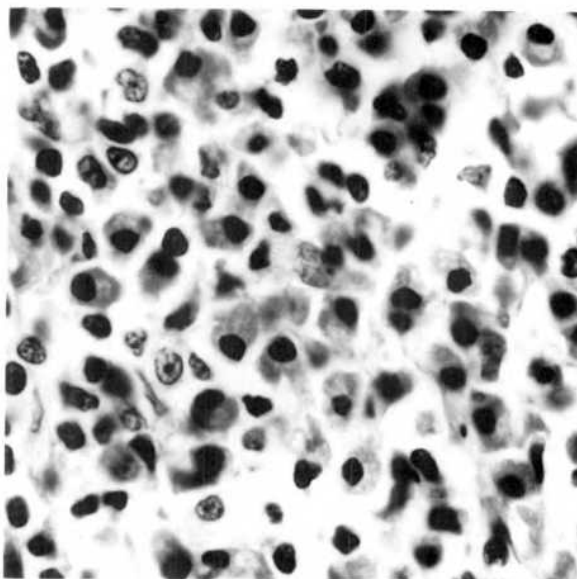


Fig. 2 Bladder biopsy showing dense plasma cell infiltrate. (H and E $\times 750$).

Comment

Plasmacytoma involving the bladder has not been previously described even in a large post mortem study of extra-osseous disease sites (Pasmantier and Azar, 1969). Intestinal involvement is also rare, especially in the absence of advanced marrow disease (Costa, 1973). The clinical presentation is also unique because myeloma usually presents with features resulting from marrow replacement, plasma hyperviscosity and/or renal tubular damage.

The clinical, urographic and cystoscopic findings in this case were consistent with but not diagnostic of bladder malignancy. This underlines the importance of random bladder biopsies in suspicious cases.

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Fig. 1 Left retrograde pyelogram showing the upper ureter and pelvis with the renal mass protruding into it. The calices are obstructed and have not filled.

Multilocular Cystic Nephroma

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Case Report

A 54-year-old female was admitted with a history of 2 episodes of haematuria. Physical examination was unremarkable. Ultrasound revealed a complex left renal mass composed of multiple cysts with a few solid areas and a retrograde pyelogram showed it to be extending into the renal pelvis, obstructing the collecting system (Fig. 1). On angiography there were irregular new vessels in the upper pole of the kidney. As a neoplasm was thought to be the most likely diagnosis, a left nephrectomy was carried out. A multiloculated cystic mass (13 cm in diameter) was found in the upper pole of a kidney weighing 610 g (Fig. 2). It protruded into the pelvicaliceal system and had caused obstruction with hydronephrosis. On microscopy the tumour was well defined and had a fibrous capsule. The cysts were lined by flattened cells with cuboidal and "hob-nail" epithelium in areas. No immature elements, striated muscle or cartilage were seen in the stroma, which contained bundles of smooth muscle.

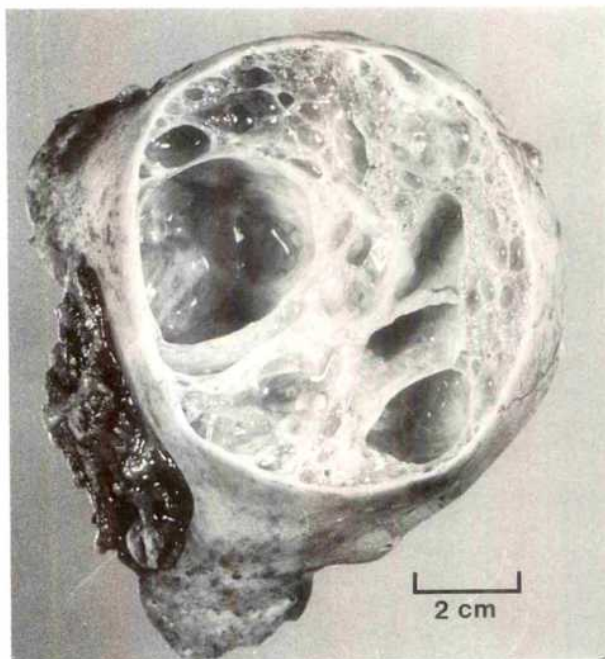


Fig. 2 Cut surface of the nephrectomy specimen showing a large cystic mass with intrapelvic herniation and obstruction.

Comment

The first case was reported by Edmunds (1892). Powell *et al.* (1951) proposed 8 criteria for the diagnosis of multilocular cystic nephroma, all of which this tumour fulfils. Over 110 cases have now been reported under a variety of synonyms including multilocular cyst, multilocular renal cyst, cystadenoma, cystic renal hamartoma, polycystic Wilms' tumour, partially differentiated nephroblastoma and cystic nephroma of childhood. There is a striking pattern of age and sex distribution (Fig. 3). Over 90% of the paediatric cases are in males aged less than 2 years; in contrast, the adult group has an overwhelming female predominance.

The biphasic distribution suggests 2 separate entities and the childhood tumour, which is related to nephroblastoma (Joshi, 1979), should be regarded as a separate entity from the benign adult tumour.

Acknowledgement

We are grateful to Mr M. Chard for photographic assistance.

References

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Powell, T., Shackman, R. and Johnson, H. D. (1951). Multilocular cysts of the kidney. *Br. J. Urol.*, **23**, 142-152.

Requests for reprints to: E. R. Nairn, Department of Histopathology, Queen Elizabeth Medical Centre, Birmingham.

Transitional Cell Carcinoma of the Urachus

D. R. LYTH and C. M. BOOTH, *Department of Urology, Colchester General Hospital, Colchester*

Adenocarcinoma of the urachus is rare, but transitional carcinoma is exceptional; this is the fourth case report.

Case Report

A 61-year-old man presented with recurrent episodes of abdominal swelling due to a lower abdominal mass shown on CT scanning (Fig. 1) as a mixed solid and

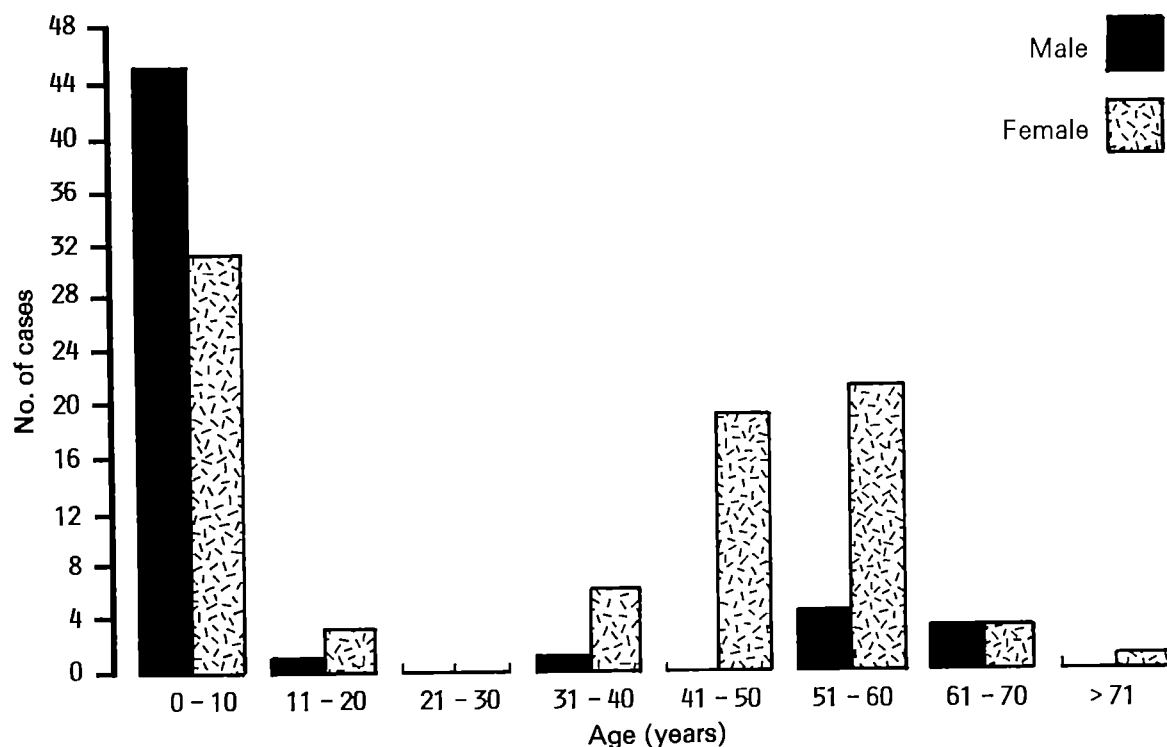


Fig. 3 Bar chart of cases plotted against age. Note biphasic pattern.

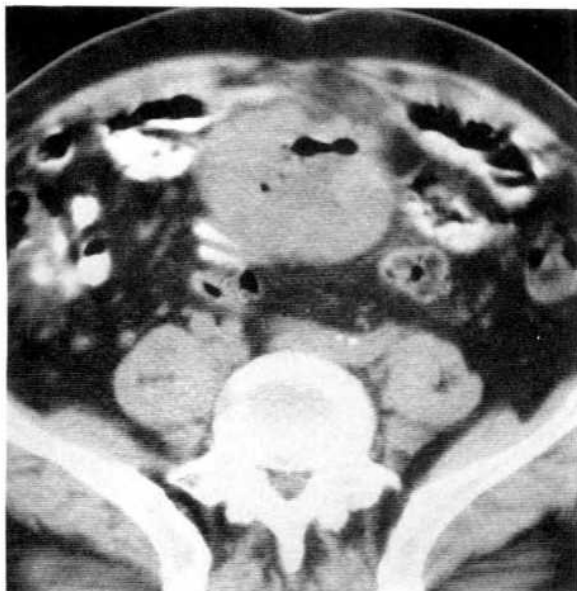


Fig. 1 CT scan of urachal tumour.

cystic tumour involving bowel and containing gas and fluid. Intravenous urography was normal and cystoscopy revealed only a benign haemangioma of the fundus of the bladder, confirmed by biopsy.

At laparotomy a 15-cm, necrotic, fragmenting urachal tumour invading sigmoid colon and ileum was excised in continuity with the bladder fundus and the umbilicus (Fig. 2).

No adjuvant treatment was given and follow-up cystoscopies remained normal; 24 months later a recurrent abdominal mass and liver metastases developed.

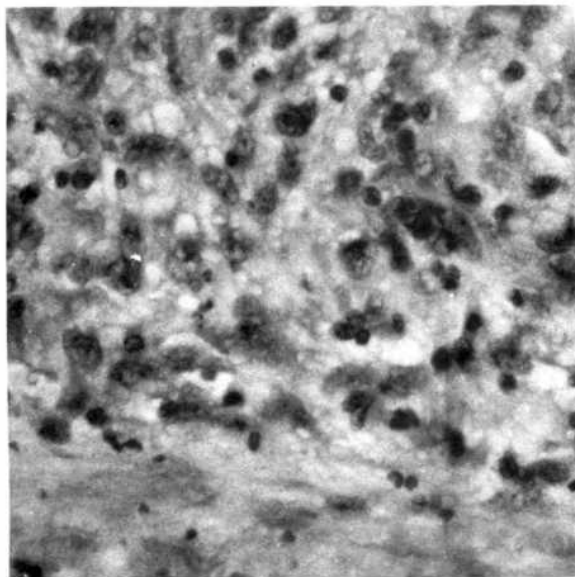


Fig. 2 Transitional cell carcinoma of urachus. (H and E $\times 600$).

After partial remission with chemotherapy the patient died 32 months post-operatively.

Comment

The urachus originates from the cloacal portion of the bladder where it joins the allantois (Begg, 1931). When the urachus remains as a muscular tube, a cuboidal or transitional epithelium may remain and undergo malignant change. Most carcinomas are adenomatous and only 3 cases of transitional cell carcinoma are reported in the English literature as accepted by criteria in the comprehensive review by Sheldon *et al.* (1984).

Urachal tumours frequently present at an advanced stage, no doubt due to their origin in an anatomically silent area, and CT scanning, as in this case, provides the best diagnostic information (Korobkin *et al.*, 1988).

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Requests for reprints to: C. M. Booth, 27 Oaks Drive, Colchester, Essex CO3 3PR.

Urethral Duplication and Chordee—A Rare Association

G. M. LAWSON and W. G. SCOBIE, *Department of Paediatric Surgery, Western General Hospital, Edinburgh*

Urethral duplication in the male is a rare abnormality. The first of 180 recorded cases was described by Aristotle. There are several varieties, each with its own mode of presentation and associated congenital abnormalities. A case of urethral duplication associated with ventral chordee is reported. This association has not been previously documented.

Case Report

A 3½-year-old boy was referred with chordee and an

adherent prepuce. There had been no difficulty with micturition.

Separation of preputial adhesions revealed a normally sited meatus at the apex of the glans and a second meatus 3 to 4 mm proximally on the ventral aspect of the glans. An 8F oesophageal catheter could be passed into the bladder through either meatus. A micturating cystourethrogram showed a double urethra as far as the membranous urethra. The bladder neck and posterior urethra were normal (Fig.). A 10F cystoscope could not be passed beyond the membranous urethra when placed in the "normal" meatus. The ventral urethra would not accept it at all. Abdominal ultrasound scan and intravenous urography showed no abnormality of bladder, ureters and kidneys. Surgical correction of the chordee is planned at a later date and the asymptomatic urethral duplication warrants no further treatment.

Comment

There have been several attempts to classify urethral duplication, the most useful classification being that of Williams and Kenawi (1975) (Table).

Urethral duplications may be in either a sagittal or a collateral plane, the former being the most common (Woodhouse and Williams, 1979). Complete duplications arise from common or separate bladder necks. Incomplete duplications arise from the posterior, prostatic or anterior urethra—the so-called "tuning fork urethrae". Abortive duplications are simple blind ending sinuses.

The mode of presentation of urethral duplication depends on the type of duplication and many are asymptomatic. Abortive duplications are the most common and often go unnoticed unless presenting with urethral discharge or recurrent urethritis.



Fig.

Table Classification of Urethral Duplication

Configuration	Course	Origin
Sagittal	"Y" duplication	Complete
	Epispadiac	Incomplete
	Hypospadiac	Abortive
	Spindle	
Collateral		Complete
		Abortive

Complete and incomplete duplications may present with troublesome double stream micturition, incontinence and urinary tract infections. Outflow obstruction can occur (Psihramis *et al.*, 1986) with acute retention of urine. Some duplications may be mistaken for epispadias or hypospadias. Others may present in the neonatal period in association with ambiguous genitalia (Psihramis *et al.*, 1986).

In most cases of duplication, the more ventrally placed urethra is structurally normal and contains the verumontanum and ejaculatory ducts. A significant proportion of urethral duplications, especially collateral ones, are associated with duplication of the pelvic organs (rectum, colon, bladder).

Most epispadiac duplications are complete and associated with widening of the pubic symphysis, dorsal chordee and bilateral cryptorchidism, a variant of the exstrophy-epispadias complex. Hypospadiac duplications are mostly incomplete but have a higher incidence of upper genitourinary anomalies.

"Y" duplications tend to be associated with more severe congenital anomalies including renal ectopia, renal agenesis, imperforate anus and vertebral and sacral abnormalities.

The embryology of urethral duplication is complex and beyond the scope of this report (Sohrabi *et al.*, 1978).

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Requests for reprints to: G. M. Lawson, Department of Paediatric Surgery, Western General Hospital, Edinburgh EH4 2XU.

Upward Migration of a J-shaped Internal Ureteric Stent

Y. KANEDA and A. KAI, *Department of Urology, Konan St Hill Hospital, Ube, Yamaguchi, Japan*

Case Report

A 36-year-old woman was treated by extracorporeal shockwave lithotripsy (ESWL) for a right renal staghorn calculus. Before the second session of ESWL, the J-shaped tip internal ureteric stent was seen in its original position (Fig. 1A). On the plain film taken the next morning, however, it was seen that the stent had migrated upwards and its lower end was in the distal ureter (Fig. 1B). Fortunately, the stent was easily removed with a basket wire catheter.

Comment

The migration of an internal ureteric stent is not uncommon. To avoid this complication a double pigtail ureteric stent is preferable (Mardis *et al.*, 1979) and we now use these stents routinely for large renal calculi on ESWL.



Fig.

Reference

Mardis, H. K., Hepperlen, T. K. and Kammandel, H. (1979). Double pigtail ureteral stent. *Urology*, **14**, 23.

Requests for reprints to: Y. Kaneda, Department of Urology, Konan St Hill Hospital, Konan, Ube, Yamaguchi 759-02, Japan.

Cystitis Glandularis—Reversal with Intravesical Steroid Therapy

P. HOLDER, R. PLAIL, M. M. WALKER and R. O'N. WITHEROW, *Departments of Urology and Histopathology, St Mary's Hospital, London*

Case report

A 35-year-old Peruvian male presented with bilateral loin pain, urinary frequency, normal renal function, bilateral uretero-hydronephrosis and partial obstruction of the distal left ureter on DTPA renogram. The urine was sterile. CT scan showed a mass in the base of the bladder. Cystoscopy revealed a fronded trigonal mass obscuring both ureteric orifices. Histology showed florid metaplasia characterised by intestinal glands in the lamina propria and in muscle, but with no epithelial dysplasia (Fig. 1). Two months later, similar tissue covering the trigone and most of the bladder neck was resected to muscle.

The hydronephrosis persisted (urea 13 mmol/l) but the metaplasia settled dramatically in response to intravesical hydrocortisone in dimethyl sulphoxide (DMSO) and pentosan polysulphate, a low molecular weight heparin.

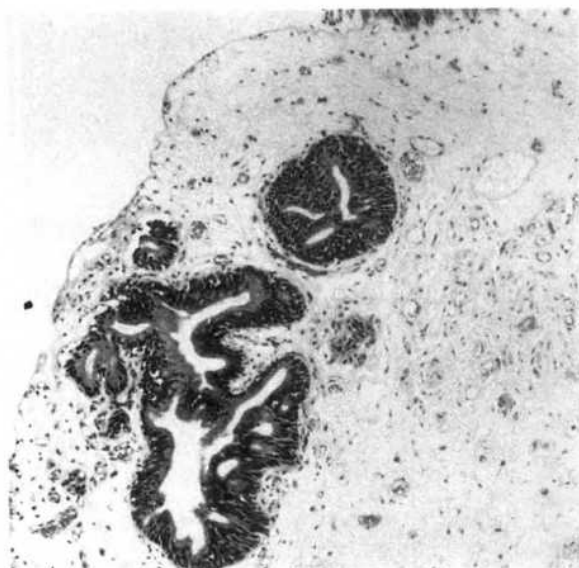


Fig. 1 Bladder mucosa showing intestinal type metaplasia in lamina propria. (H and E $\times 100$).



Fig. 2 Cystitis cystica is seen but the intestinal metaplasia is no longer present. (H and E $\times 100$).

as confirmed on biopsy (Fig. 2), with reversion to normal after 8 treatments at weekly intervals.

Thirteen months later, IVU showed left hydronephrosis and a non-functioning right kidney. Laparotomy revealed fibrous encasement of the lower ureters at the bladder wall. The left was resected and reimplanted into a Boari flap and a right to left transuretero-ureterostomy performed. Histology showed fibrosis and proliferation of ureteric muscle. The patient remains well with normal renal function.

Comment

The reversal of diffuse cystitis glandularis (Lin *et al.*, 1980) with intravesical hydrocortisone, DMSO and low molecular weight heparin is of interest and may be due to an anti-angiogenic mechanism (Ingbar *et al.*, 1985). The fibrotic process around the distal ureters at the bladder wall appeared to persist, necessitating surgical correction, but no malignancy was seen. Renal function remains stable.

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Requests for reprints to: R. O'N. Witherow, Department of Urology, St Mary's Hospital, Praed Street, London W2 1NY.

Renal Inflammatory Pseudotumour

J. S. K. GELISTER, M. JARMULOWICZ, J. DONALD, K. ANSON and R. A. MILLER, *Departments of Urology, Pathology and Radiology, Whittington Hospital, London*

Case Report

A 30-year-old male presented with right iliac fossa and loin pain. Six months previously, after an unremarkable IVU, appendicectomy had been performed for similar symptoms but the histology was normal. A tender right flank mass was now palpable and a further IVU and ultrasound revealed an 8-cm right renal mass displacing the upper ureter and pelvis. CT scan showed an apparently fluid-filled mass with a thick irregular wall compatible with an inflammatory lesion or a necrotic tumour (Fig.) and needle aspiration cytology suggested carcinoma. There was no evidence of dissemination.

The mass, which was adherent to the vena cava and duodenum, was removed by radical nephrectomy. The patient remained well 6 months later.

The tumour had a thick fibrous wall with a central gelatinous area. Microscopy showed spindle cells in a fascicular and storiform pattern in a loose myxoid stroma as well as areas of dense collagen. Many areas showed lymphoid aggregates with numerous plasma cells and eosinophils.

Comment

Only 2 previous cases of renal inflammatory pseudotumour have been reported, 1 involving the

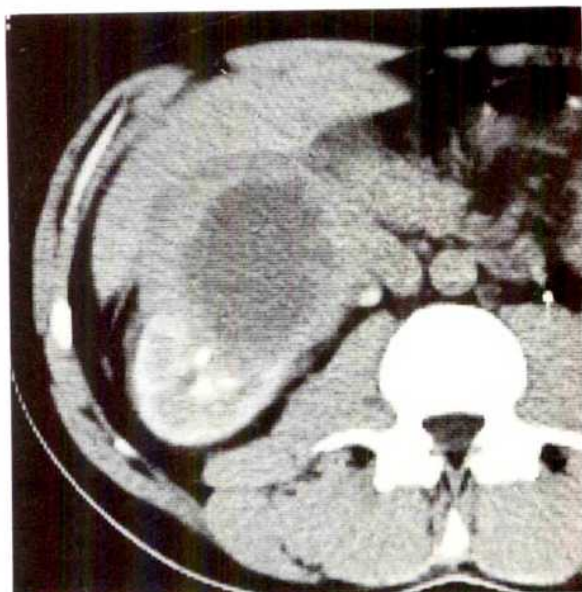


Fig. CT scan showing mass in right kidney.

renal pelvis (Davides *et al.*, 1972) and the other involving parenchyma (Fisch and Brodey, 1976). However, this condition is more frequent in other locations. These lesions, also referred to as plasma cell granulomas, masquerade as malignant growths and are often associated with a low grade fever and pain (Anthony and Telesinghe, 1986). Their aetiology is unknown; they may follow an inflammatory episode but are not associated with any specific infective agent. The diagnosis is rarely made before surgical excision, which should be curative. The present case is notable for the unusual CT appearances and for the adherence to neighbouring

structures and rapid growth over a 6-month period despite its benign nature.

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Davides, K. C., Johnson, S. H., Marshall, M. *et al.* (1972). Plasma cell granuloma of the renal pelvis. *J. Urol.*, **107**, 938–939.
Fisch, A. and Brodey, M. D. (1976). Plasma cell granuloma of kidney. *Urology*, **8**, 89–91.

Requests for reprints to: J. S. K. Gelister, Department of Urology, Whittington Hospital, St Mary's Wing, Highgate Hill, London N19 5NF.

Points of Technique

Repair of Vesical Fistulae using Lyophilised Human Dura

U. SIMSEK, M. OZYURT and B. OKTAY, *Department of Urology, Uludag University, Bursa, Turkey*

Conventional methods for the repair of benign vesical fistulae involve separation of the 2 organs, closure of the 2 openings and drainage of the bladder for an adequate period of time. The method we describe avoids extensive dissection and gives the best results when done on vesical fistulae that have a diameter of less than 2 cm and are sited far away from the trigone or the ureteric orifices.

Technique

Using the suprapubic route, the bladder is opened and the fistula exposed. The lyophilised and sterilised human dura mater patch (supplied by Braun Meslungen Co., West Germany) is incubated in normal saline for 5 min and cut 1 cm wider than the fistula. The fistula is debrided slightly, the patch is buried under the elevated mucosa and fixed to the bladder wall with 3 or 4 4/0 polyglactin sutures (Fig.). The bladder is closed in 2 layers with catgut and drained suprapubically and urethrally for 2 weeks. The menses should be postponed with progesterone in patients with vesico-uterine fistulae and antibiotic coverage is strongly recommended.

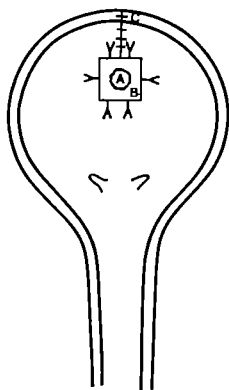


Fig. The lyophilised dura mater is in place. Intravesical view. A = fistula. B = dura mater. C = closed bladder wall.

Comment

Two patients with vesico-uterine and 2 with vesico-vaginal fistulae of at least 3 months' duration were successfully treated with this technique. At cystoscopy more than 3 months post-operatively, the lyoduraplasty was pale and slightly avascular but covered all over with epithelium. No late complications such as infection, stone formation or incontinence have occurred after an average follow-up of 2 years.

Requests for reprints to: U. Simsek, Department of Urology, Uludag University, Bursa, Turkey.

Method of Catheterising Patients with Gross Swelling of the Penis

B. N. NATHAN, *Department of Urology, Mayday Hospital, Croydon*

Male patients with gross oedema of the penis and scrotum often require catheterisation. This may be quite difficult if the foreskin is extremely swollen, non-retractile and totally obscuring the external urethral meatus. Although suprapubic catheterisation is a suitable alternative, this also may be difficult owing to abdominal wall oedema, obesity, previous scars or lack of a palpable bladder. The following method has been used to overcome this problem.

After routine skin cleansing and preparation, local anaesthetic jelly is inserted into the orifice of the prepuce. The gloved forefinger is then used to dilate this orifice. This is usually painless so long as it is done very gently. A proctoscope attached to a light source is next inserted well into the foreskin and the obturator withdrawn. The glans may be hidden some distance inside. The penis with the proctoscope is then held in the operator's left hand while the catheter is advanced into the exposed external meatus under vision. The proctoscope is then withdrawn over the catheter and the latter is advanced well into the bladder. It is important to check before the procedure that the wide end of the catheter will pass through the proctoscope.

This technique is both effective and easy to perform.

Requests for reprints to: B. N. Nathan, Department of Urology, Mayday Hospital, Croydon, Surrey, CR4 7YE.

Notices

British Association of Urological Surgeons

President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting: Scarborough. 10–13 July 1990

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Shackman Travelling Fellowship 1991

Applications are invited from Medical Practitioners registered in the United Kingdom who are Senior Registrars in an accredited training pro-

gramme in urology or Consultant Urological Surgeons of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for applications is 1 September 1990.

Further particulars from and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

Diary

1990

- May 20–24 European Nuclear Medicine Congress 1990. Amsterdam, The Netherlands. Contact QLT/Congrex, Keizersgracht 782, 1017 EC Amsterdam, The Netherlands.
- May 27–June 3 Urological Society of Australasia. 43rd Annual Scientific Meeting Darwin–Kakadu. Contact ASM Secretariat, Urological Society of Australasia, 145 MacQuarie St, Sydney 2000, Australia. Tel: 27 4461
- June 9–10 Société Belge d'Urologie: 55th Congress. Brussels, Belgium. The topic will be "Medical Films on Urology". Contact Dr F. F. Wart, C.H.U.-I.M.C.A.G., Division of Urology, Boulevard Zoe Drion 1, B-6000 Charleroi, Belgium.
- June 12 First Annual Meeting of the European Society of Paediatric Urology. Amsterdam, The Netherlands. The topic will be Posterior Urethral Valves. Contact Dr P. Mouriquand, "Le Dizenier", 11 impasse Mouillard, 69009 Lyon, France.
- June 13–16 Ninth Congress of the European Association of Urology. Amsterdam. Contact QLT Convention Services, Keizersgracht 792, 1017 AC Amsterdam, The Netherlands. Tel: 010 31 20261372
- June 18–22 Revision Course, Diploma in Urology. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
- June 24–28 Canadian Urological Association Meeting, Vancouver, British Columbia, Canada. (To be held jointly with members of BAUS). Contact Dr J. P. Collins, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada.
- July 10–13 BAUS Annual Meeting, Spa Conference Centre, Scarborough. Contact Secretariat, Royal College of Surgeons, Lincolns Inn Fields, London WC1. Tel: 01 405 1390
- September 9–11 Biannual Conference of International Society for Dynamics of the Upper Urinary Tract. Stockholm, Sweden. Contact Anne-Charlotte Kinn, Department of Urology, St Görans Sjukhus, 112 81 Stockholm, Sweden.
- October 4–5 **Urological Management of Spinal Injury. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.**
- October 16–19 25th Annual Meeting of the Egyptian Urological Association. Cairo, Egypt. Contact Dr Ahmad S. Bedair, 26 Adly Street, Flat 908, Cairo, Egypt.
- October 17–19 Advanced Stone Management Course. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
- October 25–29 Second International Congress on "The Pelvic Floor"—Update Management. Fort de France, Martinique. Contact Bureau Congress: I.F.R.U.G. "The Pelvic Floor", 2 Square La Fontaine, 2, Paris 75016, France.

- November 8–9 **Renal Failure and Transplantation. Guy's Hospital, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.**
- 1991
- January 22–25 Eighth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev Hospital, Herlev, Denmark. Contact F. Rasmussen, Department of Urology, Herlev Hospital, 2730 Herlev, Denmark.
- September 4–7 Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllői út 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016.

Those meetings in heavy print are under the auspices of BAUS.

Book Reviews

Urology Annual 1989. Volume 3. Edited by S. N. Rous. Pp. xi + 266. Norwalk, Connecticut/San Mateo, California: Appleton and Lange. 1989. Price: £54.50.

The third volume in this new annual series is every bit as good as previous volumes. Once again the editor has identified what he calls "hot topics" in urology and on this occasion erectile dysfunction and its management claim that accolade. Of the remaining 14 chapters this reviewer found fine needle aspiration of the prostate gland, radiation therapy in localised prostatic cancer, adoptive immunotherapy in renal carcinoma, and recent advances in vesicoureteral reflux to be all excellent contributions. Three chapters outside the main stream of urological topics deserve special mention—newer contrast media in urographic imaging, computers in urology, and the environment in medicine. The latter is a very disturbing chapter and contains some telling comments on the effect of competition on physicians, on the loss of influence in health care systems by physicians, and the uncertain prospects for academic urologists: these all sound very familiar. This is a very good book with well chosen and well written topics and deserves to gain a place in all urological departments and libraries.

Year Book of Urology, 1988. Edited by J. Y. Gillenwater and S. S. Howards. Pp. xvi + 309. Chicago, London, Boca Raton: Year Book Medical Publishers Inc. 1989. Price: £35.50.

Two hundred and thirty-eight abstracts comprise this volume, having been selected from more than 3000 articles reviewed. Some indication of the reason for selection is given in the introduction and one conclusion might be that the 90% not included were of little importance. Since this is possible but unlikely, then one must conclude that selection is in the eye of the beholder and the editors have drawn on some key people to evaluate articles in their area of expertise. Competition from books with a selection of reviews written by such experts must be increasing but this book remains useful for those who want a broad cover of their specialty.

The Testis. Second edition. (Comprehensive Endocrinology, Revised Series). Edited by H. Burger and D. de Kretser. Pp. xiv + 591. New York: Raven Press. 1989. Price: US\$137.50.

This second edition is from a series entitled Comprehensive Endocrinology and is aimed at a very wide

audience—embryologists, endocrinologists, urologists, paediatricians, gynaecologists, to name but some. The book is in two parts: first—embryology, physiology and biochemistry; second—clinical aspects. Chapters that will have more obvious appeal to urologists include the assessment of human sperm function, carcinoma *in situ* of the testis, vasculature of the testis, management of impotence and, perhaps, male contraception: 1988 and beyond. This is an important, up-to-date book in this field.

Clinical Renal Imaging. By W. R. Cattell, Judith A. W. Webb and A. J. W. Hilson. Pp. xiii + 218. Chichester, New York, Brisbane, Toronto, Singapore: Wiley. 1989. Price: £66.00.

This book is written by a nephrologist, a radiologist and a nuclear medicine physician and aims to define the strengths and weaknesses of the various modern imaging techniques available to solve diagnostic problems in the renal tract. The book is divided into 3 parts. The first is a comprehensive description of the techniques available for renal tract imaging. There is a concise explanation of their principles together with their strengths and weaknesses. The second part considers the most appropriate imaging techniques to investigate patients presenting with the commoner signs or symptoms of renal disease. The final part deals with particular conditions and explains the best choice of imaging techniques for diagnosis and subsequent management.

This is an attractive book with a high quality finish. The layout is clear, with adequate and helpful tables and good quality prints of radiographs. The text is concise but comprehensive, with an effective index and a helpful list of abbreviations.

Based on the authors' considerable experience, this book will be very helpful to trainee radiologists, nephrologists, urologists, and nuclear medicine physicians. It will be an asset to libraries in hospitals or other institutions with an interest in renal medicine or surgery.

Current Nephrology. Volume 12. Edited by H. C. Gonick. Pp. xii + 457. Chicago, London, Boca Raton: Year Book Medical Publishers. 1989. Price: £53.50.

Volume 12 in this excellent series of Current Nephrology takes on a greater international flavour with more authors from Europe. The 10 chapters are each an essay on some aspects of nephrology and are well written, with up-to-date references. The chapter entitled "Consequences of Urinary Tract Infections in Childhood" is particularly timely and should be read by all paediatricians and by

those who have an interest in vesicoureteric reflux. It summarises current views on the pathogenesis and natural history of this disorder and also illustrates the important gaps in our knowledge. Hugh de Wardener provides a lucid account of natriuretic hormones and the roles that they might play in disorders of sodium homeostasis. The chapter illustrates all too well our extensive knowledge of individual factors but our current inability to provide plausible hypotheses to account for their interactions. The chapters on potassium metabolism and water metabolism are also excellent reviews of current thinking in these fields. The chapter on divalent ion metabolism updates many of the rapid advances in this field in the past 10 years.

I was a little disappointed in some of the later chapters on various aspects of peritoneal dialysis, haemodialysis and related techniques and clinical transplantation. These topics are so well covered in other books and reviews that the rather compressed accounts here are less satisfactory to the nephrologist. On the other hand, they would provide an excellent review for those physicians and surgeons working outside dialysis and transplant units but who are called upon to look after these patients from time to time. The sections on haemofiltration and haemoperfusion would be particularly useful to physicians or anaesthetists in intensive care units.

Chlamydia. By P.-A. Mårdh, J. Paavonen and M. Puolakkainen. Pp. xiv + 370. New York: Plenum Publishing Corporation. 1989. Price: US\$ £50.00.

This is an interesting and topical book. *Chlamydia trachomatis* is one of the major sexually transmitted pathogens in the world today. In some countries in the continent of Africa, the rate of fallopian tube obstruction is such that whole populations are threatened and in many cases it seems that chlamydial infection is responsible. Ocular trachoma is still a major cause of blindness worldwide and a high priority is to develop vaccines against this organism.

This book is topical because of the current interest in the epidemiology of *Chlamydia* and also because of the basic laboratory research which is now under way to produce vaccines. For anyone who is interested in this pathogen, this book is essential. There is a short section on genital tract infection in the male and in general the book is well referenced.

Essential Urology. By N. Bullock, G. Sibley and R. Whitaker. Pp. vi + 342. Edinburgh: Churchill Livingstone. 1989. Price: £9.95.

This is an excellent little book at a very reasonable price of £9.95. The authors' aim is to provide a short, up-to-

date textbook primarily for medical students "to aid them in grasping the fundamental concepts behind current urological practice". They achieve this aim admirably. They also hope that nurses and surgical trainees will find useful practical hints and there is no doubt that they will.

The book has an impressive uniformity of style despite the multiple authorship and the coverage is very even, showing that the authors have gone to considerable lengths not to be "over-enthusiastic" about their own particular interests.

There is considerable competition these days, with several excellent books intended for medical students, but this seems to be the best to have appeared so far.

Renal Cystic Disease. AFIP Atlas of Radiologic-Pathologic Correlation. Fascicle I. Edited by D. S. Hartman. Pp. xiv + 160. Philadelphia: Saunders. 1989. Price: £34.00.

This book is the first in a new series of atlases from the AFIP in Washington correlating radiological and pathological findings. Renal cystic disease is a difficult and confusing subject but in this book the diseases under consideration are presented in a clear and orderly manner. There are a number of very useful tables which enhance the succinct text. The value of an atlas depends to a great extent on the quality of the illustrations and it must be said that the radiological pictures are generally outstanding. The photographs of pathological specimens, many of them gross specimens, are of more variable quality (all of the colour photographs are grouped together at the front of the atlas). Each chapter has a helpful list of references. Anyone wishing to understand or refer to cystic disease of the kidneys in all its forms can consult this book with pleasure and profit.

Uro pathology. Volumes 1 and 2. Edited by G. S. Hill. Pp. xiii + 622 (Volume 1), 623-1380 (Volume 2). New York, Edinburgh, London, Melbourne: Churchill Livingstone. 1989. Price: £195.00.

This handsome and impressive 2-volume publication covering the whole field of urological pathology is the work of 9 contributors under the editorship of Gary S. Hill. Not only is it comprehensive in its coverage but it is at the same time a mine of information difficult to obtain from any other single source.

There are no weak sections in this book and there are some especially noteworthy features, such as the chapters on congenital anomalies and anomalies of differentiation and development of the urinary tract. The chapters (by Gary Hill) on urinary tract infections and renal infections and the important subject of vesicoureteric reflux are all dealt with in a most impressive manner. All neoplastic

diseases are comprehensively covered and the chapters on the prostate gland are especially helpful in the more controversial areas.

The book is extremely well illustrated and almost all of the illustrations are of a very high standard. Each chapter has a full list of references.

It is hard to find fault with this book and every medical library and pathology department will probably wish to acquire a copy.

Management of Advanced Cancer of Prostate and Bladder. EORTC Genitourinary Group Monograph 4. (Progress in Clinical and Biological Research, Volume 260). Edited by P. H. Smith and M. Pavone-Macaluso. Pp. xxiii + 658. New York: Alan R. Liss. 1988. Price: US\$120.00.

This book is the fourth of the EORTC Genitourinary Group Monographs. It represents an important record of an EORTC Symposium in October 1986 and the Fifth Course in Urological Oncology at Erice in December 1986. The extent of the material is comprehensive, with detailed coverage of European activities but also contributions from Canada, the United States, Australia and Egypt. This volume, as with the other monographs by the EORTC Genitourinary Group, is an invaluable record of the high level of activity in urological oncology.

Systemic Therapy for Genitourinary Cancers. Edited by D. E. Johnson, C. J. Logothetis and A. C. von Eschenbach. Pp. xxiii + 394. Chicago, London, Boca Raton: Year Book Medical Publishers. 1989. Price: £59.00.

The choice of treatment for various malignancies continues to widen and the urologist needs to be aware of the many changes in strategy that have occurred in the past 5 years. A well read urologist might feel that he/she has already seen much of the information presented in this book—and it is probably true.

This book is in 2 parts—the first dealing with urinary tract tumours (urothelial and renal) and the second dealing with genital tumours (prostate, penile and germ cell). The emphasis is to report the relevant studies using cytotoxic agents, hormones and interferons. The chapters are written by acknowledged experts, almost all of whom are reporting their own experience. The weakness of this approach is that it is difficult to gain a true picture of the relative merits of these treatments and to redress this, the editors offer a commentary after each major section: these are useful but could have been expanded with benefit for the non-expert. It is recommended that the reader starts with these 4 commentaries and then pursues the details in the individual articles. Inevitable quibbles arise in a book of this scope but overall it is highly recommended for those concerned with this important and often perplexing part of urology—*i.e.* almost all urologists.

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REVIEW

Video-endoscopy: the Remote Operating Technique

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Video-endoscopy (or the remote operating technique) has evolved as a response to the demands of modern endoscopic urology. The microvideo camera and television monitor are used by the surgeon to view the operating field instead of looking directly through the telescope.

The increasing sophistication of urological equipment and the development of the concept of minimally invasive surgery has resulted in the urologist spending much of his time performing endoscopic procedures. In many district general hospitals only 20% of the total operating time is now devoted to open surgery.

Conventional Endoscopy: Problems

Conventional endoscopic surgery demands intense concentration and is physically taxing because of the bizarre postures which are unwittingly adopted by the urologist performing transurethral, ureteroscopic and percutaneous manoeuvres. This imposes significant strain on the surgeon's cervical and lumbar spine. Whitaker *et al.* (1983) drew attention to the problem of cervical spondylosis as an occupational hazard of the urologist, and while their findings may be inconclusive, few senior urologists would disagree with the hypothesis. For the sceptic it is instructive to make a video tape concentrating on the movements of the surgeon during a routine endoscopic procedure! The author has had countless personal communications from urologists throughout the world, following demonstrations of the remote operating technique, which express concern at the vulnerability of their spinal columns to the stresses imposed by lengthy endoscopic sessions. The use of mobile adjustable chairs and powered tilting operating tables, which the surgeon can control, may be helpful. The remote operating technique is, however, a more practical and effective solution.

The intimate contact between the patient's

perineal region and the urologist is not only aesthetically unacceptable, but also potentially hazardous to the well-being of the surgeon. The dangers are many and varied. A famous Leeds urological quiz slide: "What is the lesion on the face of the visiting urologist?" Answer: "A diathermy burn from faulty insulation of an endoscope sheath," emphasises the importance of adequate maintenance of endoscopic equipment. Yet most urologists have encountered sparking or even smoke issuing from the diathermy contact port of the resectoscope. In addition, the present generation of light sources with a power output of up to 500 watts exposes the retina to the risk of trauma and should be used with caution. An excellent demonstration of one danger of these powerful beam generators was provided by a videotape from the Institute of Urology, London, which shows a surgical drape being set alight by a "carelessly" placed fibre optic light cable. Fortunately, this hazard is now recognised and many, but not all, manufacturers produce a cold light source. Nevertheless, the intensity of the photon bombardment of the retina remains a hazard and most urologists are aware of temporary visual impairment in the dominant eye after a prolonged endoscopic procedure. The long-term effects of repeated exposure to high intensity light, which may include macular degeneration, are largely unknown, but are at present being evaluated (Miller, personal communication). More recently, great concern has been engendered by the potential contamination of the operating surgeon and theatre staff by blood-stained effluent and bodily secretions, which in theory may result in the transmission of infection. This must be a most serious consideration when performing endoscopic manoeuvres on HIV positive patients. Prior to the advent of AIDS, the spraying of the surgeon by blood-stained effluent, as a result of the patient suddenly straining, was regarded with levity and even by some anaesthetists as just punishment for slow operating technique. This situation has now changed with the recognition

of the possible serious consequences to theatre personnel and appreciation that contamination may unknowingly occur in up to 33% of endoscopic operations (McNicholas *et al.*, 1989). It is, therefore, the duty of the surgeon to take every precaution to protect himself and his theatre colleagues and thus the current vogue for not wearing masks, gowns or adequate drapes, since these do not significantly influence infection rates in patients, must be reconsidered in view of the vulnerability of the operator. Lightweight resistant gowns, masks with built-in visors to protect the eyes and purpose-built urological drapes may be the accessories of the future. However, one of the most important prophylactic measures must be to remove the surgeon as much as possible from intimate contact with the patient.

A Solution

An interest in television as a medium for teaching and recording in urology led to the realisation that the television camera could be used, not only for display purposes, but also as an effective accessory operating instrument.

It became apparent that operations could be performed efficiently by viewing the image on a small television monitor suitably positioned in front of the surgeon, rather than by peering through the telescope. The magnified image on the television monitor readily allowed identification of landmarks and the different tissue characteristics, the recognition of which is necessary for safe and effective endoscopic surgery. The most attractive feature, however, was that for the first time the urologist enjoyed a sense of freedom from the bonds which had caused him to spend lengthy periods in close proximity to the perineum of his patient. The increased postural comfort of operating with a straight back and neck and the facility to operate with the hands and arms in a natural position, rather than perpetually above shoulder level, justify the description "the armchair prostatectomy".

Present Position

Video-endoscopy is now used extensively in orthopaedic and gynaecological surgery and the advantages in the facilitation of training and in the participation of all theatre personnel in endoscopic operations make acquisition of the technique well worthwhile. Video-endoscopes which abolish the need for a complicated lens system are already in use in some general surgical theatres. These instruments, however, are of greater diameter than

urological endoscopes and thus permit realisation of the "chip on the tip" concept.

Our efforts were originally directed to perfecting videoprostatectomy, the commonest major urological operation, but it has become apparent that all areas of endoscopic surgery are amenable to the application of the video technique. The exception may be fibre optic flexible instruments, which pose special problems due to light polarisation. Routine endoscopy, bladder neck surgery, resection of bladder tumours, any of the ureteric manipulations, insertion of stents, ureteroscopy and, in particular, percutaneous surgery can all be performed effectively with greater comfort and safety using the microvideo camera. The magnification of the image on the monitor is particularly helpful in ureteric manipulation. Moreover, the facility to share the video image with other members of the operating team leads to greater understanding and more effective assistance during operating sessions. As Yachia (1987) comments, "The acceptance of video-endoscopy as a standard procedure will revolutionise the teaching of endoscopic surgery by showing all the procedures in real time with all the problems encountered, how to avoid them and how an experienced operator overcomes them".

Audience Participation

An additional bonus of operating using a video monitor was that for the first time everyone involved in the operating suite could see exactly what the surgeon was doing. This led to greater involvement and commitment by all theatre personnel to what had previously been dreary, protracted, endoscopic sessions. The benefit to trainee surgeons, nurses, theatre technicians, students and anaesthetic colleagues was immediately apparent. The time honoured anaesthetic riposte to surgical complaints of inadequate hypotension causing poor vision, "Well, it's alright at my end," was no longer heard as colleagues appreciated the surgeon's difficulties, and the greater understanding led to more effective anaesthetic technique.

There were also disadvantages. The original tube cameras were relatively heavy and cumbersome, restricting the free movement of the resectoscope by impinging on the patient's thighs and requiring counterbalancing systems to eliminate weight and drag which interfere with the surgeon's touch sense. They were, moreover, relatively fragile and could not be easily disinfected.

Rapid advances in video technology combined with miniaturisation techniques saw the emergence

of a new generation of microvideo cameras, the charge couple device (CCD camera). These resolved many of the difficulties, with a weight of only 25 to 100 g and dimension slightly larger than the eyepiece of the telescope. They are attached by a lightweight cable to a remotely placed camera controller unit which adjusts to the colour temperature of the light source and has a colour painting facility. Gross adjustment of colour is achieved by the monitor controls. These cameras are totally immersible, thus permitting adequate disinfection in standard activated glutaraldehyde solution.

Caveat

In order to achieve the best results with these remarkable cameras, it is important to have an adequate light source and to use a telescope in optimum condition. The human eye is very forgiving, the video camera totally impartial!

Before purchasing a microvideo operating system it is essential to understand one's personal requirements and to have an adequate demonstration of the capability of the various systems in one's own operating theatre. Guidelines which may be helpful in choosing an appropriate purchase and avoiding disappointment have recently been published (O'Boyle *et al.*, 1989).

The key to success is to use good quality, compatible equipment which has been properly set up for colour and resolution, thus eliminating diathermy radiofrequency interference.

As with any new technique, there is a learning curve for remote operating video-endoscopy, usually a rapid process for an experienced endoscopic surgeon. Younger colleagues in particular seem to adapt more readily to high technology endoscopic operating, while there is greater reluctance by some more senior members of the profession to change firmly established habits. The private world of endoscopic surgery, however, has been invaded and much of the mystique removed. The ultimate benefit is to the surgeon who now finds himself in a more relaxed environment, akin to that of open surgical operations.

Some find orientation initially difficult due to the macro image and feel more comfortable with a beam splitter attachment, which allows them to peep down the telescope and check the visual image. This is rapidly discarded with increasing experience. Others have suggested that they lose depth sense when operating from the image on a video monitor. This seems strange when one considers the conventional monocular instrument.

Future Projects

We are undoubtedly living in exciting times as a result of progress in urological technology. Dramatic technical advances have been made in ultrasonics. The new generation of user friendly sector scanners and intravesical and rectal multiplanar probes means that for most working purposes real time ultrasonography can be conducted by the urologist himself. Adequate instruction and training in ultrasound technique and interpretation will become part of the curriculum for higher surgical training for future generations. A fascinating exercise is to monitor transurethral prostatic resection using a multiplanar rectal ultrasound scanner. Perhaps this will ultimately prove a more objective measurement of residual prostatic tissue than even the much venerated digital examination.

Robotic prostatectomy, although at present confined to the "vegetable" kingdom, shows some promise. Computer-controlled robotic movements are extremely precise. It may well prove possible to programme the computer by feedback from a multiplanar probe which evaluates the dimensions of the prostatic adenoma and effectively delineates the surgical capsule. A similar system using an endovesical ultrasound probe to guide a laser beam has the potential to deal with bladder tumours, thus eliminating another repetitive and time-consuming surgical chore.

In conclusion, the concept of video-endoscopy as a remote operating technique has evolved as a result of developments in microchip technology. It is a safe and effective method of conducting endoscopic operations in a variety of surgical disciplines, including urology. Thus it seems reasonable to predict that with further sophistication of medical equipment, remote controlled operations may well become a reality in the future.

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Low Calcium Diet in Idiopathic Urolithiasis: A Risk Factor for Osteopenia as Great as in Primary Hyperparathyroidism

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Summary—The bone mineral content of the radius was measured in 32 male renal stone formers, 18 of them presenting with idiopathic urolithiasis and 14 with primary hyperparathyroidism, a disease known to disturb bone metabolism. The idiopathic stone formers had been on regular treatment with a low calcium diet. The bone mineral content of the radius was reduced to a similar level in both groups of patients. The data suggest that idiopathic stone formers on a low calcium diet are at risk of osteopenia; the factors which could lead to a negative calcium balance included uncompensated renal hypercalciuria, hypophosphataemia and exaggerated serum levels of 1,25-dihydroxyvitamin D. To treat idiopathic hypercalciuria, thiazide diuretics, which reduce the renal excretion of calcium and have been shown to be beneficial for bone, seem safer than a low calcium diet.

It has been confirmed by Fuss *et al.* (1983) that idiopathic renal stone formers often present with a reduced bone mineral content (Alhava *et al.*, 1976). Bone loss could be related to idiopathic hypercalciuria, a common feature in idiopathic urolithiasis. Together with other workers (Lawoyin *et al.*, 1979), we have found a low bone mineral content in conjunction with so-called renal idiopathic hypercalciuria (Pak *et al.*, 1975), also with “absorptive” idiopathic hypercalciuria, and even in the absence of hypercalciuria (Barkin *et al.*, 1985). Additional data from a large group of idiopathic renal stone formers demonstrated that the reduction in bone mineral content was much more pronounced in patients on a long-term low calcium diet than in patients on a free diet (Fuss *et al.*, 1989). In that study we also found that the factors which could lead to a negative calcium balance in idiopathic stone formers on a low calcium diet included uncompensated “renal” hypercalciuria, hypophosphataemia, exaggerated serum levels of 1,25 (OH)₂ vitamin D.

The aim of the present study was to identify these factors more clearly in idiopathic renal stone formers on a low calcium diet and to compare this situation with urolithiasis resulting from primary hyperparathyroidism, a disease known to disturb bone metabolism.

Patients and Methods

The study included 32 Caucasian male stone formers; 18 patients, aged between 32 and 70 years (mean 52) presented with idiopathic urolithiasis and 14, aged between 24 and 68 years (mean 51) had primary hyperparathyroidism. All were ambulatory, had normal states of nutrition, normal renal glomerular function and had received no treatment known to interfere with calcium metabolism. The idiopathic stone formers (ISF) were included in the study consecutively, irrespective of their urinary calcium excretion. They had been on regular treatment with a low calcium, low oxalate diet for 10.0 ± 0.7 years. Their calcium intake was estimated by a dietician to be 8.8 ± 0.5 mmol (SEM).

In order to identify renal and absorptive idiopathic hypercalciuria more clearly (Pak *et al.*, 1975), blood and urine measurements were performed after a standard reduction of calcium intake for at least 1 week in all patients and also in 15 normal men aged between 22 and 63 years (mean 36).

Serum and urine concentrations of creatinine, calcium and phosphate and serum alkaline phosphatase activity were measured routinely. Serum immunoreactive parathyroid hormone (iPTH) was measured using different antisera and the results expressed as a percentage of the normal upper limit obtained with the corresponding radioimmunoassay; 25-hydroxyvitamin D (25 OHD) and 1,25-dihydroxyvitamin D (1,25 (OH)₂D) were measured in serum (Bouillon *et al.*, 1980) and cyclic AMP and hydroxyproline in fasting urine (Tovey *et al.*, 1974; Delfosse *et al.*, 1975).

Bone mineral content (BMC) was measured in all patients by single photon absorptiometry (Cameron and Sorensen, 1963) at 3 cm (distal BMC) and 8 cm (proximal BMC) from the styloid process of the radius. Results were normalised for age and sex using the conversion in Z-scores (value measured minus the mean value from age and sex-matched normal subjects, divided by the standard deviation).

One-way analysis of variance and Scheffe's test (Scheffe, 1959) were used to compare mean biochemical values. BMC Z-scores from the patients were compared with normal values using Student's *t* test of compatibility of the means.

Results

Biochemical values

Serum levels and urinary excretion of calcium and phosphate. As expected, serum calcium was normal in idiopathic stone formers and increased in hyperparathyroid patients (Fig. 1A). On a similar low calcium diet, idiopathic stone formers and hyperparathyroid patients presented with comparable degrees of hypercalciuria over a 24-h collection period as well as in the fasting state (Fig. 1B and D). A number of patients from the 2 groups showed normal urinary excretion of calcium under this dietary regime. Fasting hypercalciuria, suggestive of renal hypercalciuria when serum calcium is normal (Pak *et al.*, 1975), was present in one-third of idiopathic stone formers. Serum levels of phosphate (Fig. 1C) were reduced in hyperparathyroidism ($P < 0.005$) and to a lesser extent in idiopathic

urolithiasis ($P < 0.025$), in which the levels were lower than normal in 17% of the patients.

Parathyroid function. Hyperparathyroid patients presented in most cases with the expected increase ($P < 0.005$) in serum iPTH concentrations (Fig. 2A) and in urinary excretion of cyclic AMP (Fig. 2C), whereas no difference was found between idiopathic stone formers and the normal subjects.

Metabolites of vitamin D. Serum concentrations of 25 OHD (Fig. 2D) and 1,25 (OH)₂D (Fig. 2B) were not significantly different between the groups; the concentrations of 1,25 (OH)₂D were not significantly higher than in the normal subjects on the same low-calcium diet. However, when compared with the same normal subjects on a free diet (dots in the hatched area), 1,25 (OH)₂D levels were higher than the upper normal limit in 43% of the idiopathic stone formers and in 50% of the hyperparathyroid patients.

Indicators of bone turnover. Serum alkaline phosphatase activity and fasting urinary excretion of hydroxyproline (Fig. 3) were increased in both groups of patients ($P < 0.05$).

Bone mineral content

As shown in Figure 4, a reduction in bone mineral content ($P < 0.01$) was observed in both groups of

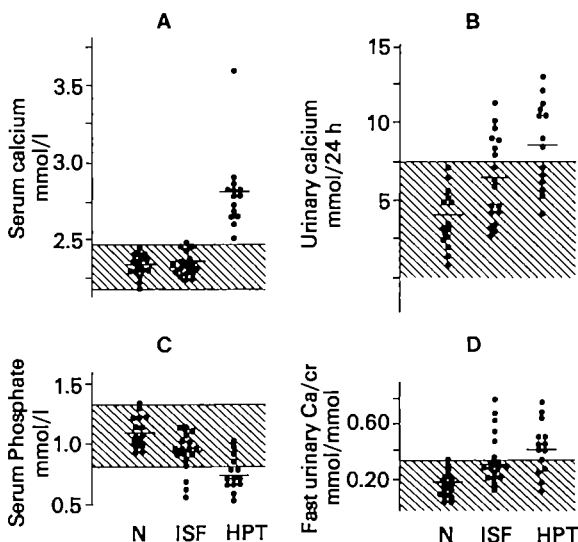


Fig. 1 Data obtained in normal subjects (N), in idiopathic stone formers (ISF) and in primary hyperparathyroidism (HPT). Hatched areas correspond to the normal range (mean $\pm$ 2 SD) of values.

patients at both sites of the radius. This decrease was as pronounced in idiopathic stone formers on a sustained low calcium diet as in the hyperparathyroid patients. No correlation was found in idiopathic stone formers between their BMC and factors believed to induce a low BMC, *i.e.* fasting hypercalciuria, (suggestive of renal hypercalciuria), hypophosphataemia and elevated serum levels of $1,25(\text{OH})_2\text{D}$.

Discussion

The most salient feature of this study was that the reduction in bone mineral content in idiopathic renal stone formers on a long-term low calcium diet was as pronounced as that observed in hyperparathyroid stone formers.

Accelerated bone turnover is common in primary hyperparathyroidism. The well known effect of parathyroid hormone on osteoclastic resorption is reflected by increased excretion of hydroxyproline and calcium in the urine, whereas elevated alkaline phosphatase activity in serum reflects increased osteoblastic activity. As a result, patients with primary hyperparathyroidism usually present with some reduction in bone mineral content (Fuss *et al.*, 1983; Martin *et al.*, 1986; Rao *et al.*, 1988).

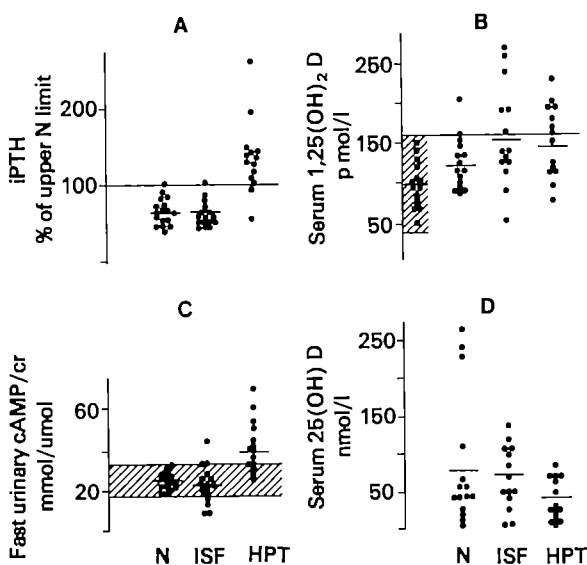


Fig. 2 Data obtained in normal subjects (N), in idiopathic stone formers (ISF) and in primary hyperparathyroidism (HPT). iPTH: immunoreactive parathyroid hormone, percentage of upper normal limit; cAMP/cr: ratio of cyclic AMP on creatinine; $1,25(\text{OH})_2\text{D}$: $1,25$ dihydroxyvitamin D, dots and hatched area in the margin: range of serum $1,25(\text{OH})_2$ levels in the normal subjects on a free diet; 25OHD : 25 hydroxyvitamin D.

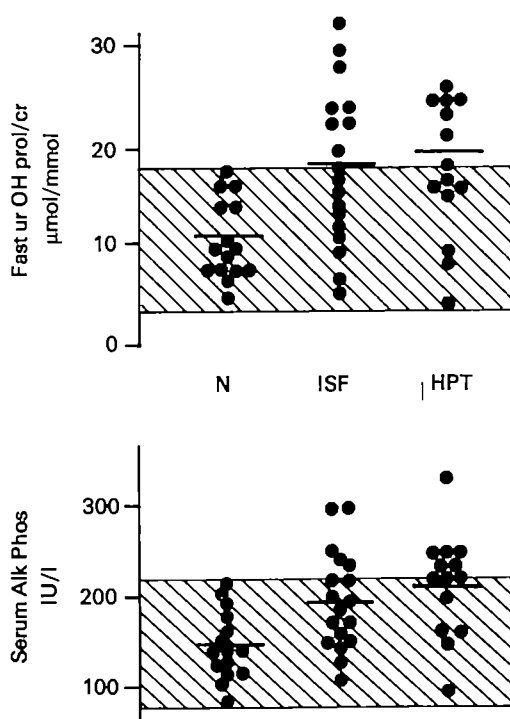


Fig. 3 Alk.phos: alkaline phosphatase activity; ur OHprol/cr: ratio of hydroxyproline on creatinine in urine.

High values of serum alkaline phosphatase activity and urinary excretion of hydroxyproline were present also in idiopathic stone formers on a low calcium diet, suggesting increased bone turnover in this condition.

Normocalcaemic hyperparathyroidism, either primary or secondary to renal hypercalciuria (Coe *et al.*, 1973), is not a convincing explanation for the bone abnormalities in idiopathic stone formers in the present study, since serum levels of iPTH and urinary excretion of cyclic AMP were normal in virtually every case.

Idiopathic "renal" hypercalciuria, if not compensated by an appropriate calcium supply, will lead to a negative calcium balance. Hypophosphataemia in idiopathic urolithiasis was shown to be associated with increased resorption and decreased formation of bone (Bordier *et al.*, 1977). Elevated circulating levels of $1,25(\text{OH})_2\text{D}$ can induce bone resorption and result in negative calcium balances, especially if associated with a low calcium diet (Maierhofer *et al.*, 1984). One or more of these situations were present in a number of our idiopathic stone formers.

Thus several mechanisms could lead to a negative calcium balance and to a reduction in the mineral content of bone in idiopathic stone formers on to a

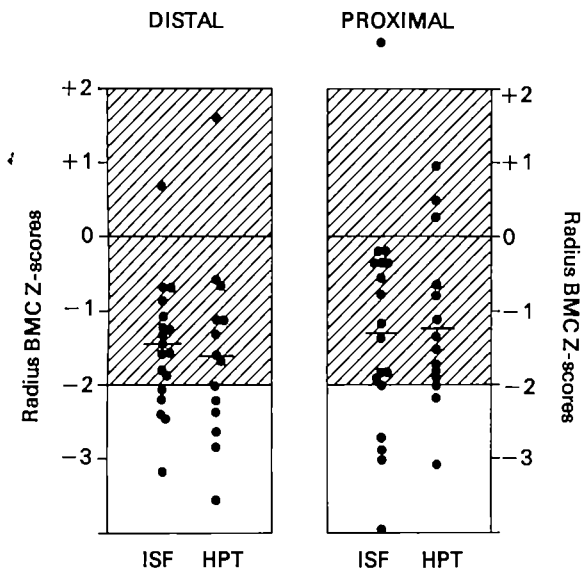


Fig. 4 Bone mineral content expressed as Z-score (value measured minus the mean value in age and sex-matched normal subjects, divided by the standard deviation of their results).

low calcium diet. The present study shows that this reduction could be as pronounced as in hyperparathyroid patients. An increase in the bone mineral content of the radius was observed after surgical correction of primary hyperparathyroidism (Martin *et al.*, 1986) and we wonder if idiopathic stone formers, on a low calcium diet for years, would also be able to increase their bone mineral content with an appropriate supply of calcium and phosphate. In the treatment of idiopathic hypercalciuria, thiazide diuretics, which reduce the renal excretion of calcium and are beneficial for bone (Ray *et al.*, 1989), appear safer than a low calcium diet.

Acknowledgements

This work was supported by the Fonds de la Recherche Scientifique Médicale de Belgique. The authors thank the nurses of the Endocrine Unit and the Stone Clinics, and A. Bergans, N. Michiels, R. Lefevre for their technical assistance.

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Renal Transplant Biopsy using Real Time Ultrasound Guidance

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Summary—We describe a safe method of percutaneous renal transplant biopsy using real time ultrasound guidance. The method provides a good histological sample, is straightforward and has a low complication rate.

Renal transplant biopsy is an essential diagnostic tool in the management of acute graft dysfunction but is not without risk to both the graft and the patient. The technique is routinely performed and a safe and reliable method is therefore essential. Percutaneous biopsy using a modified Vim-Silverman (Tru-cut) needle is the standard method used in most centres but the techniques vary considerably. In particular, several different methods of localising the transplanted kidney have been described and include simple palpation (Buselmeier *et al.*, 1976), fluoroscopy (Pillay and Kurtzman, 1973), metal tagging (Matthew *et al.*, 1968) and ultrasound (Appel *et al.*, 1981).

The ideal transplant biopsy technique will yield renal cortical tissue of good size and quality without damaging the renal allograft. We have devised a technique in which real time ultrasound scanning is used to guide the biopsy needle selectively into the renal cortex with the aim of avoiding the potentially dangerous medulla and hilum of the kidney.

Method

Prior to biopsy the INR should be in the normal range and the diastolic blood pressure should be less than 100 mmHg. The procedure is performed under aseptic conditions. The transplanted kidney is localised and orientated using ultrasound scanning. In this unit an Aloka SSD-630 real time

machine is used with a fully sterilisable 3.5 MHz linear array probe. A transverse or longitudinal section of the kidney is demonstrated in a position which is suitable for easy manipulation of the biopsy gun and needle. The ultrasound probe is held steady throughout the procedure by an assistant. The skin and subcutaneous tissues down to the capsule of the transplanted kidney are anaesthetised by the local infiltration of 1–2% lignocaine solution. A scalpel blade (no. 11) is used to pierce the skin over the transplant to facilitate smooth passage of the biopsy needle. We use a 14 gauge Tru-cut biopsy needle (Travenol Laboratories Incorporated, Deerfield, USA) mounted in the Biopsy gun (Radiplast AB, Uppsala, Sweden). This is an automatic firing device which works by a spring loaded mechanism (Lindgren, 1982). The Tru-cut needle is introduced through the subcutaneous tissues and down to the capsule of the kidney under ultrasound control. The needle is carefully passed through the fibrous pseudocapsule of the transplanted kidney. This capsule presents variable resistance, depending on the age of the transplant, and with long-standing organs is often quite thick. The biopsy track and needle tip can be seen very clearly ultrasonically and this allows precise targeting (Fig.). The biopsy needle tip is positioned just underneath the pseudocapsule and the angle of attack adjusted so that a superficial cortical biopsy is taken.

Following biopsy, firm pressure is applied over the biopsy site for 5 min. A pressure dressing is then applied and the patient is kept on strict bed rest for 12 h. Intensive observation of the pulse and

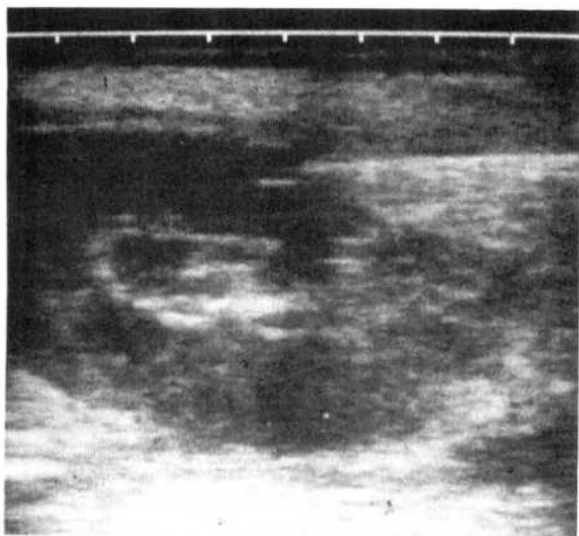


Fig. Ultrasound guided needle biopsy of renal transplant.

blood pressure is made during this time interval. Serial urine samples are displayed at the bedside to judge the presence and progress of macroscopic haematuria.

Results

During the last 2 years, 123 renal transplant biopsies have been performed using this technique. In some patients more than 1 biopsy core was obtained during a single procedure and 212 cores of renal tissue were taken. All tissue was examined by a consultant histopathologist. Renal tissue was present in 203 biopsies (96%) and renal cortex in 188 (89%). The glomerular count per biopsy core was 14.7 ± 9.3 (mean $\pm$ SD). Slight macroscopic haematuria was noted after 9 biopsies (7%). This responded to conservative management in all cases and there were no cases of allograft loss as a direct result of the biopsy procedure.

Discussion

The use of both the Biopsy gun and the ultrasound scanner are essential to the success of the method. The Biopsy gun performs the 2-stage cutting action of the Tru-cut needle mechanically and we believe that this improves both the size and quality of the tissue core obtained when compared with the manual Tru-cut technique.

The use of real time ultrasound allows accurate orientation of the biopsy procedure so that the renal vessels and ureter are avoided. The ultrasound scan also clearly distinguishes between renal cortex and medulla and, with experience, selective biopsy of the renal cortex can be achieved. This ensures a good glomerular count and avoids damage to the blood vessels in the medulla and hilum of the kidney.

Ultrasound guided biopsy of the transplanted kidney is a simple and safe procedure which produces a high percentage of adequate biopsies.

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Diuretic Ultrasound. A Non-invasive Technique for the Assessment of Upper Tract Obstruction

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Summary—A study was made of the diagnostic reliability of renal ultrasound with a diuretic in the evaluation of upper tract obstruction. The test comprised an initial renal ultrasound examination followed by the intravenous injection of 250 ml physiological saline with 40 mg frusemide; further ultrasound scans were carried out from 5 to 150 minutes later. A total of 67 patients was studied and the results were compared with those of diuretic intravenous urography, diuretic renography and, in some cases, the Whitaker test. Dynamic ultrasound with a diuretic showed a sensitivity of 94%, specificity of 94%, positive predictive value of 91% (obstructive), negative predictive value of 96% (non-obstruction) and a total diagnostic capacity of 94%.

Introduction

Ultrasound of the upper urinary tract has shown high sensitivity in the diagnosis of hydronephrosis with a low incidence of false positives, usually due to pathology in the renal sinus (lipomatosis, parapelvic cysts) and an equally low number of false negatives, usually related to intermittent hydronephrosis (Ziviello *et al.*, 1986). Difficulty in providing a functional evaluation has been the main disadvantage of ultrasound in assessing upper urinary tract obstruction, but dynamic ultrasound with a diuretic now provides this information. The technique described by Rosenfield and Taylor (1976) has recently gained wider acceptance but still plays a complementary role to other diagnostic techniques used to assess upper urinary tract obstruction, such as diuretic intravenous urography, diuretic renography and the Whitaker test (Rosenfield and Taylor, 1976; Bono *et al.*, 1987; Lombi *et al.*, 1987). The present study was carried out on 67 patients with suspected obstructive pathology of the upper urinary tract.

Patients and Methods

The technique is simple. A basal renal ultrasound examination is performed initially, the kidneys being studied in different planes to obtain a clear picture of the renal collecting system. When the best image has been obtained, the scanning plane remains constant for the rest of the procedure. After the initial scan, 250 ml physiological saline and 40 mg frusemide are injected intravenously (over 15–20 min). Renal ultrasound at 5, 10 and 15 min is then repeated. The patient is subsequently asked to urinate. Further scans at 30, 45, 60, 90, 120 and 150 min are made in both the upright and the supine positions. A similar procedure is followed with young children, the infusion of physiological saline being related to the patient's weight (5 ml/kg) and the frusemide dose being 0.5 to 1 mg/kg. Assessment is based on the relative increase in the pelvicaliceal diameters and the time taken for the renal collecting system to return to its initial dimensions. Sixty-seven patients were studied, 3 of them with single kidneys, making a total of 131 renoureteric units.

There were 50 females and 17 males in the series, ranging in age from 7 to 77 years (average 38.5); 6 of the kidneys studied were in children. The

indications for examination are shown in the Table. All patients underwent a diuretic IVU and a diuretic renogram. A Whitaker test was performed when the response was equivocal and also when patients had already had a nephrostomy or during surgery.

The assessment of upper tract obstruction was based on the results of these examinations together with clinical data. Three groups of patients were identified: (1) normal, (2) non-obstructive stasis (pelviureteric hypotonia) and (3) moderate or severe obstruction. The results of this diuretic ultrasound test were compared in these groups to assess its reliability.

Results

It was possible to identify several typical ultrasonographic patterns. The normal state is characterised either by a complete absence of change in the renal collecting system following diuretic injection or by a moderate increase in pelvicaliceal diameters, with a return to the basal condition in less than 60 min (Fig. 1). In non-obstructive stasis the return to the basal condition always occurs between 60 and 90 min (Fig. 2). In mild obstruction the ultrasound pattern is characterised at the initial examination by absent or mild pelvicaliceal dilatation and by a variable increase after the diuretic, with a return to the former condition within 90 to 150 min (Fig. 3). In severe obstruction, pyelectasis can be absent to moderate in the basal condition but once induced by the diuretic it fails to return to the former condition within 150 min (Fig. 4). In other cases of severe obstruction, an established hydronephrosis,

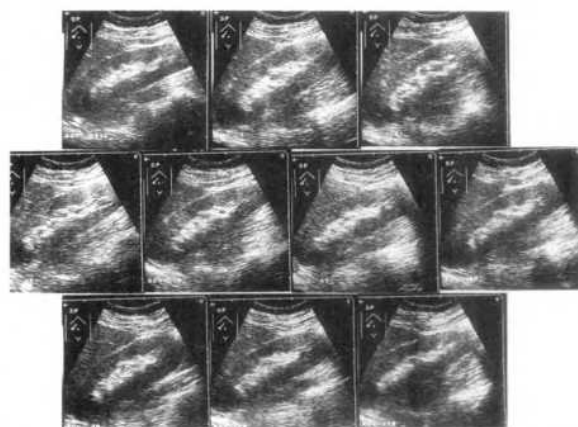


Fig. 1 Moderate increase in pelvicaliceal diameters after diuretic injection with return to basal condition within 60 min. Normal condition.

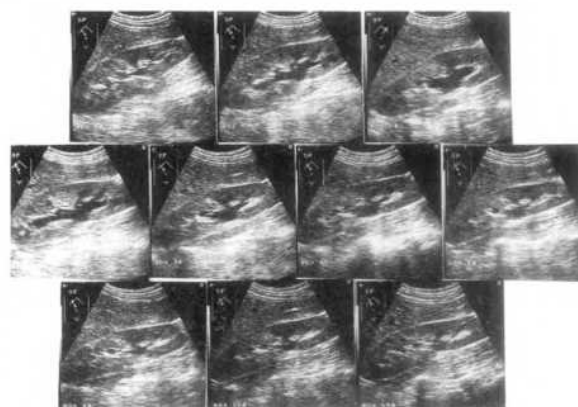


Fig. 2 Increase in pelvicaliceal diameters after diuretic injection and return to basal condition within 90 min. Non-obstructive stasis.

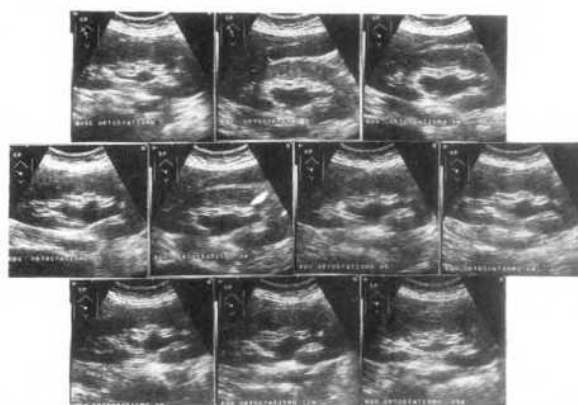


Fig. 3 Moderate pelvicaliceal dilatation at basal ultrasound with increase in pelvicaliceal diameters after diuretic injection and return to basal condition within 150 min. Low grade obstruction.

Table Indications for Dynamic Ultrasound

	<i>No. of patients</i>
Pelviureteric junction stenosis	14
Lumbar and iliac ureteric stenosis	5
Pre-vesical ureteric stenosis	5
Upper urinary tract stones	4
Bladder wall fibrosis	1
Post-operative follow-up	11
Renal ptosis	9
Ectopic kidney	2
Atonic ampullectasis (IVU and ultrasound report in symptomatic patients)	12
Hydronephrosis in pregnancy	1
Pelviureteric duplication	1
Differential diagnosis of renal pelvic echo-poor areas (ultrasound report)	2
Total	67



Fig. 4 Absence of pelvicaliceal dilatation at basal ultrasound with increase in pelvicaliceal diameters after diuretic injection and no return to basal condition within 150 min.

already present at the basal examination, increases after the diuretic and fails to return to the former condition within 150 min (Fig. 5). In patients with intermittent hydronephrosis, the ultrasonographic picture is characterised by marked pelvicaliceal dilatation alternating with periods of normality (Fig. 6).

The renal collecting system return to the basal condition within 60 min (indicating normality) in 75 renoureteric units. This was correct in 74 units (99%); only 1 false negative was found in a patient with low grade obstruction. In units which returned to the basal condition within 60 to 90 min, dynamic ultrasound correctly diagnosed non-obstructive stasis in 17 (85%). There was 1 false negative (low grade obstruction) and 2 false positives (normal urinary tracts). A return to the basal condition between 90 and 150 min was noted in 9 units; in 8 of these (89%) low grade obstruction was confirmed



Fig. 5 Phases of dilatation and normalisation of renal collecting system after diuretic injection. Intermittent hydronephrosis.

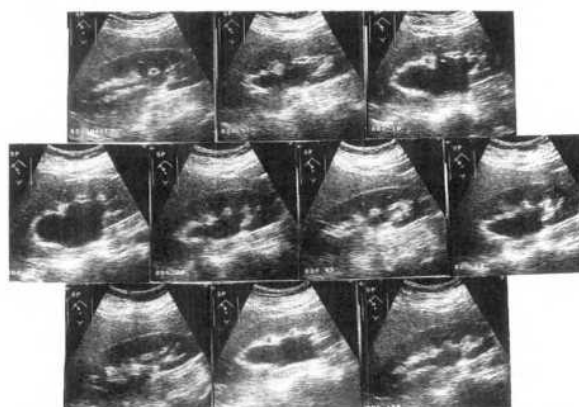


Fig. 6 Hydronephrosis at basal ultrasound with increase in pelvicaliceal diameters after diuretic injection and no return to basal condition within 150 min. Severe obstruction.

and there was 1 false negative (11%) in a patient with severe obstruction; there were no false positives. In 24 units there was no return to the basal condition within 150 min and in 21 of these (88%) high grade obstruction was confirmed. In this group there were 3 false positives (1 non-obstructive stasis and 2 low grade obstructions). Three intermittent hydronephroses were correctly diagnosed. Four kidneys that were functionally excluded with both standard IVU and renography were also studied. Two patients were found to have a moderate increase in pelvicaliceal diameters after the diuretic test. In the other 2 there was no change. The results of the diuretic ultrasound test gave a sensitivity of 94%, a specificity of 94%, a negative predictive value (non-obstruction) of 96%, a positive predictive value of 91% (obstructive) and total diagnostic capacity of 94%.

Discussion

Correct management of upper tract obstruction depends on its diagnosis and the degree of obstruction. These are not always easy to establish—hence the number of tests employed, including IVU with a diuretic, colic IVU renography with or without a diuretic challenge and renal isotope scanning (O'Reilly *et al.*, 1979). The Vela-Navarrete and Whitaker tests are considered the most sensitive but they are invasive (Whitaker, 1979; Whitaker and Buxton, 1984). With any 2 of the 3 following tests—diuretic IVU, diuretic renography and the Whitaker test—an accuracy rate of 95% is possible.

Mistakes in the diagnosis of obstruction can occur in patients with acute and chronic renal failure, vascular pathology, infection and reflux,

when using standard radiological and radio-isotope techniques. In cases of partial obstruction, intermittent hydronephrosis and in patients with a high compliance pelvis, even the Whitaker test may be unreliable. It is hoped that the diuretic ultrasound test will be helpful in these difficult areas. The initial results are encouraging but larger series are required in order to standardise the technique and confirm its validity.

The test is useful in patients with upper tract stasis on a standard IVU to determine whether or not this is due to obstruction. It is also useful in patients with intermittent hydronephrosis or reduced renal function. It has helped to differentiate echo-poor lesions at the renal pelvis (such as parapelvic cysts and lipomatosis) from pyelectasis. Important information has been gained in pregnant patients and in the regular follow-up of children after operations on the renal tract.

After diuresis has provoked a complete washout of contrast material or radio-isotope, the diuretic IVU and renogram are no longer valid tests. Diuretic ultrasound is readily repeatable and does not involve radiation. It may be used during an episode of renal colic and also allows assessment of renal cortical thickness.

The highest number of correct diagnoses (99%) was found in the normal group, where the technique also showed high sensitivity (94%) and a high negative predictive value (96%). Its reliability was high in the presence of obstruction, with a specificity of 94% and a positive predictive value of 91%. The smallest number of correct diagnoses occurred in patients with non-obstructive stasis and pelviureteric hypotonia (85%).

Preliminary results lead us to believe that the diuretic ultrasound test will occupy a useful place

in the investigation of suspected obstructive uropathy. Additional advantages include its non-invasive nature, the absence of contraindications, technical ease, repeatability and wide application.

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Adrenal Cysts: Diagnosis and Management

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Summary—We present 7 patients (5 adult females and 2 neonate males) with adrenal cysts. The cysts included 1 hydatid, 1 lymphatic and 5 pseudocysts. Three cysts were diagnosed pre-operatively and all were resected surgically. The existence of true epithelial cysts of the adrenal gland is doubted by many authors; the present series includes most types of adrenal cyst.

Adrenal cysts are a rare occurrence. Greiseliuss reported the first case in 1670. Scattered case reports appeared until 1959, when Abeshouse *et al.* reviewed 155 cases from the literature, including 3 of their own. The total number of cases reviewed by Foster (1966) rose to 220, including 1 of his own. With the advent of computed tomography (CT) and ultrasound (US) scans (Copeland, 1983), more cysts are being discovered incidentally. We describe 7 types of adrenal cyst treated surgically at Jordan University Hospital between 1977 and 1989.

Patients and Methods

The records of 27 patients who underwent adrenalectomy between June 1977 and June 1989 were reviewed. Adrenal cyst was the indication for adrenalectomy in 7 patients (Table). They included 2 neonate males (6 and 12 days old) and 5 adult females aged between 40 and 78 years. Three cysts were discovered incidentally: 2 neonates were found to have right upper abdominal masses during investigation for sepsis and jaundice which proved to be physiological, and in a 60-year-old female the cyst was found during US studies for gallbladder disease; a 6-day-old neonate had a history of difficult vaginal delivery. Four patients were symptomatic and had upper abdominal and loin pain. One had had a left nephrectomy for calculi several years earlier and another had undergone previous surgery for retroperitoneal hydatid disease with a

discharging sinus in the left iliac fossa (LIF). An abdominal mass was felt in a 78-year-old female and hepatomegaly was detected in a 40-year-old female.

Laboratory tests showed leukocytosis in a patient with recurrent infected hydatid disease and an erythrocyte sedimentation rate (ESR) above 100 mm in the 78-year-old female, who proved later to have a malignant cyst. Serum electrolytes were normal and hormonal studies, requested in 3 patients, were also normal. Casoni's test and echinococcus antibody titres were evaluated in 3 patients and were positive in 1.

Radiological studies showed peripheral curvilinear calcification (Fig. 1) in a 44-year-old female at the site of previous nephrectomy. Two patients had stippled calcification in the right hypochondrium; a neonate also had a non-functioning right kidney and a 78-year-old had, in addition, distorted upper calices in the right kidney and absence of neovascularisation on renal arteriography (Fig. 2). US and CT scans were done in 5 patients and all showed cystic retroperitoneal swellings.

A pre-operative diagnosis of adrenal cyst was made in 3 cases: (1) in a patient with recurrent hydatid disease the tract of a discharging sinus from the LIF extended upwards behind the left kidney to a left adrenal cyst (Fig. 3); (2) in a neonate, new hyperdense areas were seen on a repeat ultrasound which rightly suggested a haemorrhagic cyst (Fig. 4); (3) a 60-year-old female was found to have a right adrenal cyst during US studies of the gallbladder. In the other 4 patients

Table Adrenal Cysts

<i>Year</i>	<i>Age</i>	<i>Sex</i>	<i>Presentation</i>	<i>Imaging studies</i>	<i>Final diagnosis</i>
1977	44 years	F	Abdominal and loin pain. L. nephrectomy	Retroperitoneal cyst with curvilinear calcification. ? Hydatid cyst	Adrenal pseudocyst
1980	12 days	M	Sepsis. Abdominal mass	Stippled calcification. Non-functioning R. kidney. ? Neuroblastoma	Adrenal pseudocyst due to infarction
1983	78 years	F	Abdominal and loin pain. Abdominal mass. ESR > 100	Stippled calcification. Distorted upper calices. No neovascularisation. ? Renal cyst	Cystic cortical carcinoma
1988	40 years	F	Abdominal and loin pain. Hepatomegaly	US and CT: ? liver hydatid cyst	Adrenal pseudocyst
1988	6 days	M	Physiological jaundice. Abdominal mass	US and CT: adrenal mass. Repeat US: haemorrhagic cyst	Haemorrhagic adrenal cyst
1989	50 years	F	Discharging sinus LIF. Previous surgery for hydatid cyst	CT: adrenal cyst with communicating tract to LIF	Hydatid cyst
1989	60 years	F	Gallbladder disease	US: gall stones and adrenal cyst	Lymphatic cyst

the diagnosis was made at operation. Two cysts were diagnosed pre-operatively as hydatid cysts. The 78-year-old patient was thought to have a renal cyst due to distorted upper calices; she had mixed echoes on US, stippled calcification and a high ESR, yet the malignant nature of the cyst was missed due to absence of neovascularisation on the arteriogram. The fourth patient, a 12-day-old infant, was diagnosed as having a neuroblastoma.

All patients underwent surgery through abdominal incisions. Adrenalectomy was achieved easily

in 4 cases. Additional nephrectomy was done in a neonate with an adherent non-functioning right kidney; splenectomy was indicated during excision of a hydatid cyst of the left adrenal gland. Excision of an adrenal cyst, proved to be malignant at operation, was followed by right nephrectomy and excision of a segment of inferior vena cava with reimplantation of the left renal vein into a dacron graft.

Results

Pathologically, all cysts proved to be adrenal; 5 were on the right and 2 on the left. They included a hydatid cyst, a lymphatic cyst and 5 pseudocysts. In the latter group were a cyst due to degeneration in an adrenal cortical carcinoma, 2 cysts thought to be due to previous trauma following left nephrectomy in a 40-year-old female and after difficult delivery in a neonate; the fourth pseudocyst developed in an infarcted adrenal which was accompanied by evidence of infarction in the adjacent kidney, and the cause of the fifth cyst was not known.

One neonate died soon after surgery from uncontrolled sepsis. The 78-year-old female with a malignant cyst developed deep venous thrombosis and repeated wound infection and died from sepsis 6 months after surgery. The other 5 patients recovered well and are symptom-free 3 months to 12 years post-operatively.



Fig. 1 X-ray abdomen showing peripheral curvilinear calcification in left adrenal cyst.

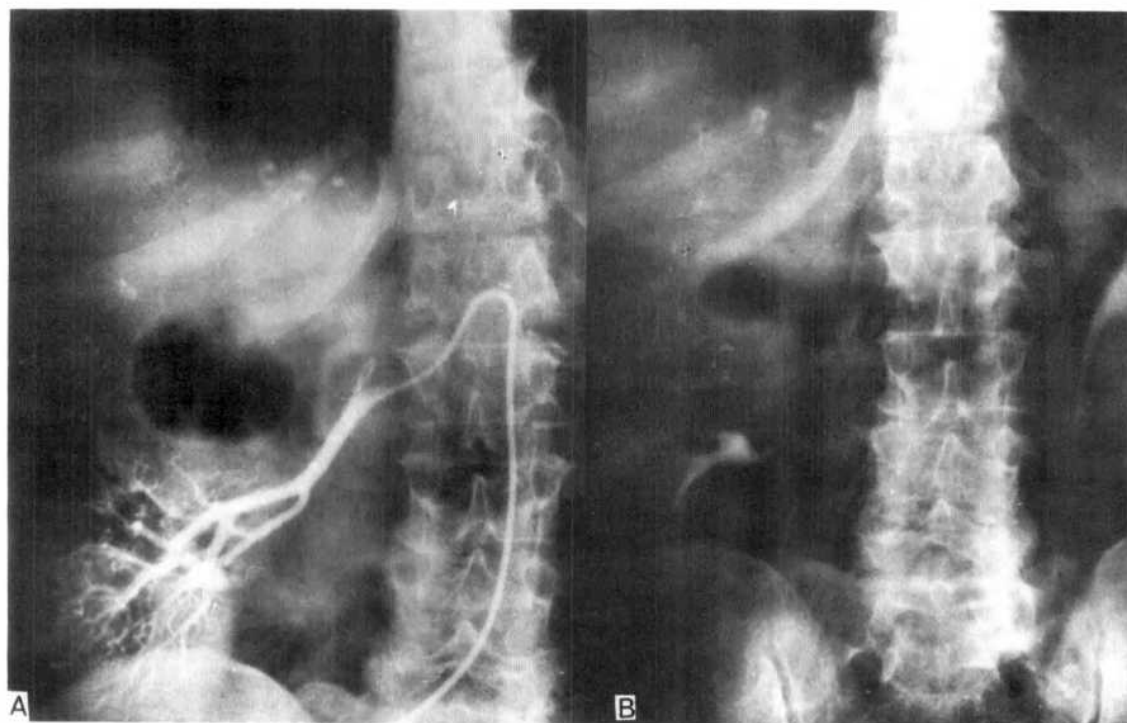


Fig. 2 (A) Right renal arteriogram with absent neovascularisation above kidney. Note scattered calcification. (B) IVU showing right kidney pushed downwards with distorted upper calices.

Discussion

Adrenal cysts are rare and their incidence in autopsy studies ranges from 0.064% (Wahl, 1951) to 0.18% (Hodges and Ellis, 1958). Copeland (1983) found 5 cysts in 51 patients with adrenal masses discovered incidentally on CT scan. Adrenal cysts occur at all ages, from birth to 80 years, with a peak in the third to sixth decades (Abeshouse *et al.*, 1959; Esquivel and Grabstald, 1965; Tehrani *et al.*, 1965; Foster, 1966; Cerney *et al.*, 1970). The female to male ratio is 2:1 in some reports (Abeshouse *et al.*, 1959; Cerney *et al.*, 1970), inconclusive or equal in others (Foster, 1966; Mikail and Kirshman, 1968). The present series included 2 neonate males and 5 adult females and their ages ranged from 6 days to 78 years.

Adrenal cysts are usually asymptomatic and many are discovered at autopsy (Wahl, 1951; Hodges *et al.*, 1958; Abeshouse *et al.*, 1959; Foster, 1966). They seldom cause adrenal hypofunction in infants (Moore and Cermak, 1950), Cushing's syndrome (Brindley and Chisholm, 1951) or pheochromocytoma (Ellis *et al.*, 1952; Cheema *et al.*, 1981). A correct pre-operative diagnosis was made in 3.2 to 7.2% of patients (Abeshouse *et al.*, 1959;

Foster, 1966). Symptoms related to adrenal cysts include vague upper abdominal or loin pain, gastrointestinal upsets and abdominal mass. Acute abdomen and/or a tender mass occur occasionally when intracystic haemorrhage, rupture or infection occur (Stewart and Lester, 1962; Foster, 1966; Pasciak and Cook, 1988). The cyst may fill the abdomen to such an extent that it is diagnosed as an ovarian cyst (Foster, 1966). Three of our patients were correctly diagnosed pre-operatively and 4 were diagnosed at surgery. Adrenal cysts were symptomatic in 4 of our adult patients who had abdominal and loin pain with acute exacerbations in a patient with a discharging sinus from an infected hydatid cyst. An abdominal mass was palpated in the 78-year-old female and incidentally in the 2 neonates, who were initially thought to have a neuroblastoma.

A soft tissue swelling with curvilinear calcification is seen occasionally on plain abdominal films (Levison, 1933; Palubinska *et al.*, 1959; Gordon *et al.*, 1960); it denotes a cystic lesion rather than a neoplasm when the calcification is stippled (Foster, 1966; Cerney *et al.*, 1970), as in our elderly patient, although such calcification is present in organised haematoma (Cheema *et al.*, 1981; Copeland, 1983)

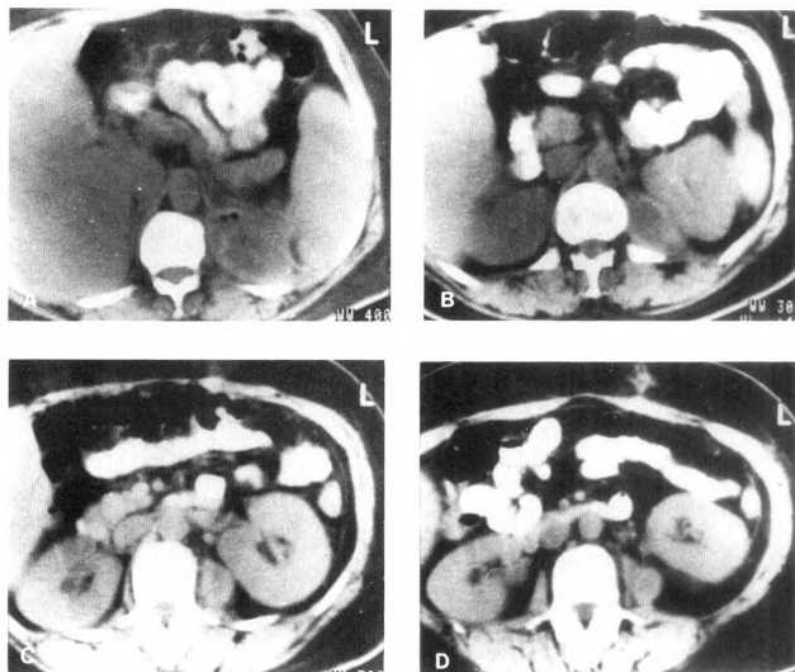


Fig. 3 CT scan showing hydatid cyst in left adrenal gland (A) extending behind the left kidney (B) forming a tract (C and D).

or infarct, as in one of our neonate patients. IVU usually shows downward displacement and rotation of the related kidney, which occasionally has distorted upper calices (Foster, 1966; Cerney *et al.*, 1970). Barium studies of the gastrointestinal tract may show displacement of stomach and colon

anteriorly, downwards, and to the other side due to a large cyst (Abeshouse *et al.*, 1959; Esquivel and Grabstald, 1965; Foster, 1966; Cerney *et al.*, 1970). Neovascularisation on angiography suggests malignancy, although it is sometimes absent (Copeland, 1983). The absence of neovascularisation and the

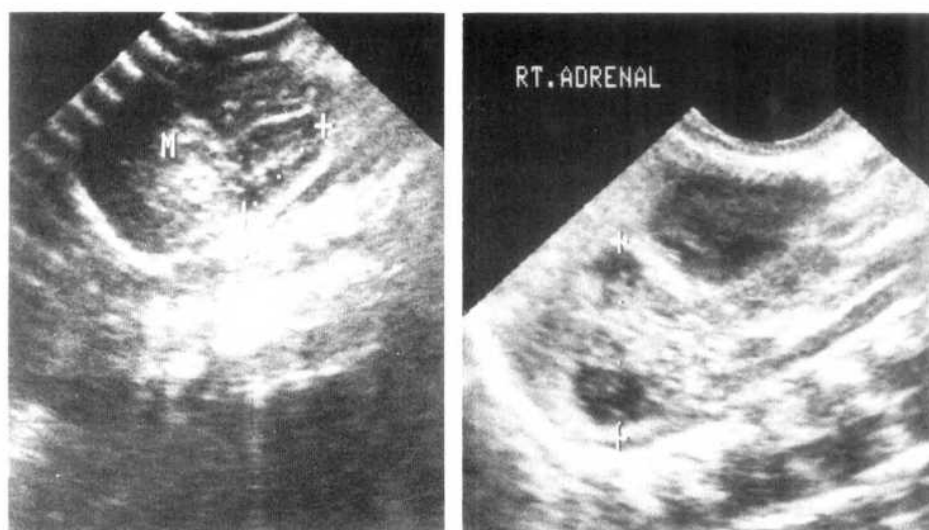


Fig. 4 (A) US showing echogenic adrenal mass above right kidney (M). (B) US showing development of new hyperdense areas (+) in the right adrenal gland reported as new haemorrhages.

distortion in the upper calices of the right kidney led us to believe that our elderly patient had a renal cyst. US and CT scans are useful diagnostic tools and many adrenal masses are discovered incidentally (Copeland, 1983; Wood *et al.*, 1987). These studies were positive in 5 of our patients. There were mixed echoes in the 78-year-old female which, together with the high ESR, should have alerted us to the possibility of malignancy. US was also very useful when it was repeated and showed the development of new hyperdense areas in the adrenal gland leading to the correct diagnosis of a haemorrhagic cyst in the 6-day-old neonate.

Complete blood counts may show low haemoglobin and haematocrit levels if there is heavy intracystic bleeding (Pasciak and Cook, 1988), leukocytosis in infected cysts (Foster, 1966), as in our infected hydatid cyst, eosinophilia in parasitic cysts and a high ESR in malignant cysts, as in our elderly patient. Electrolytes and hormonal studies are usually normal except on the rare occasion where hypoadrenocorticism is present (Moore and Cermak, 1950), or pseudocysts in functioning tumours are the cause (Brindley and Chisholm, 1951; Ellis *et al.*, 1952).

Foster (1966) divided adrenal cysts into 4 groups: (1) parasitic (echinococcal) cysts (7%); (2) epithelial cysts (9%), including true glandular, embryonal cysts and cystic adenomas; (3) endothelial cysts (45%), including lymphatic cysts, lymphangiomas and haemangiomas; (4) pseudocysts (39%) due to infarction or haemorrhage in the adrenal gland, or cystic degeneration in benign or malignant adrenal neoplasms. The existence of true epithelial cysts is doubted by many authors (Foster, 1966). Thus this study, although small, presents most types of adrenal cyst. Hydatid disease is endemic in Jordan (El-Muhtaseb, 1984) and our case represents a single occurrence of hydatid cyst in the adrenal gland in 250 (0.4%) hydatid cysts in various organs treated at this hospital. The incidence is therefore similar to the 0.5% reported by Barnett (1943).

All cysts in our patients were unilateral (4 on the right side and 2 on the left). However, adrenal cysts are seldom bilateral (Levison, 1933; Moore and Cermak, 1950) and they have no predilection for either side (Abeshouse *et al.*, 1959; Foster, 1966), except perhaps in adrenal haemorrhage in neonates, which is more common on the right side, possibly because of the susceptibility of the adrenal gland to compression between the liver and spine due to birth trauma (Kuhn *et al.*, 1971); this may have occurred in 1 of our neonates who had a difficult delivery.

The treatment of adrenal cysts (Abeshouse *et al.*, 1959; Foster, 1966) depends on the symptoms and size of the cyst, the occurrence of complications and the underlying pathology. Under the guidance of CT and US scans, asymptomatic non-functioning cysts can now be aspirated percutaneously (Copeland, 1983; Wood *et al.*, 1987). Indications for surgery include large and complicated cysts, parasitic, functioning and malignant cysts (Abeshouse *et al.*, 1959; Foster, 1966). Malignant cysts are rare (Schmieden and Peiper, 1950; Brindley and Chisholm, 1951; Plaut, 1962) and may be distinguished by a high ESR, aspiration cytology, neovascularisation on arteriography (Copeland, 1983) and the presence of mixed echoes on ultrasound. Excision of adrenal cysts in patients who do not have a phaeochromocytoma is reported to bring the blood pressure back to normal and may be taken into consideration (Foster, 1966; Cheema, *et al.*, 1981). Surgical excision can usually be achieved through an abdominal or a loin incision (Foster, 1966) and occasionally by a thoraco-abdominal approach (Pasciak and Cook, 1988). All of our patients were treated surgically through abdominal or flank incisions. In 4 cases the cysts were easily excised. Nephrectomy was required in 2 patients, splenectomy in 1 and excision of a segment of inferior vena cava in a third because of adhesions or direct invasion. Five patients are alive and well and 2 died of sepsis.

Adrenal cysts are seen occasionally by the surgeon and urologist. With the advent of better imaging techniques such as US and CT scans and magnetic resonance imaging, the diagnosis of adrenal cysts is possible pre-operatively and this was evident in our last 3 patients (Table). The distinction between malignant and benign adrenal cysts can still be difficult and underlying carcinoma should be suspected in patients with a high ESR, mixed echoes on ultrasound, stippled calcification on plain radiography and neovascularisation on arteriography. It should be emphasised that the last 2 radiological signs may be misleading and it is hoped that aspiration cytology will differentiate more accurately between benign and malignant cysts.

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Treatment of Ureteric Colic. Intravenous versus Rectal Administration of Indomethacin

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Summary—A randomised multicentre clinical trial was undertaken to compare the effect on pain of indomethacin administered either intravenously or rectally to 116 patients with ureteric colic. Adverse reactions were also assessed.

Of the patients receiving the intravenous injection, 48/53 (91%) achieved good pain relief (*i.e.* no supplementary analgesia was required) 30 min after administration, compared with 46/63 (73%) receiving the enema. Significantly more side effects occurred in the group treated intravenously.

It was concluded that indomethacin administered as an enema was less effective than the intravenous form, but it should be regarded as a good alternative in the treatment of ureteric colic.

The pain caused by the passage of a ureteric stone results from increased pelviureteric pressure (Risholm 1954; Kiil, 1957) which produces increased tension in the pelvic and ureteric wall (Holmlund and Svanvik, 1982).

Potent inhibitors of prostaglandin synthesis such as indomethacin (Holmlund and Sjödin, 1978) and diclofenac (Lundstam *et al.*, 1982) relieve renal colic effectively when given parenterally. Parenteral administration, however, has the disadvantage of requiring either admission to hospital or the presence of medical staff before pain relief can be achieved. Oral medication is not suitable because of the nausea and vomiting that often accompany acute ureteric colic. A better alternative would seem to be rectal administration, which has none of these disadvantages.

Bioavailability studies (Jensen, 1985) have shown comparability between indomethacin 100 mg given as a rectal solution and 50 mg given intravenously. Using these dosages and routes of administration, we assessed indomethacin in terms of efficacy and safety in the treatment of ureteric colic.

Patients and Methods

The inclusion criteria for this multicentre, double-blind, randomised trial were clinical symptoms of ureteric colic, age range 18 to 75 years, and informed consent. Exclusion criteria are listed in Table 1.

Safety was assessed in all patients receiving treatment.

The efficacy of the drug was analysed statistically only when the diagnosis had been confirmed either by intravenous urography or by spontaneous passage of the stone. Of the 423 patients registered, 265 were excluded for 1 or more of the reasons listed in Table 1. There was no statistically significant difference in age, sex and weight of these 265 patients and the 158 who were included in the study. The diagnosis could not be verified in 42/158 patients and so the statistical analysis was based on 116 patients; 53 of these received indomethacin intravenously and 63 received it as an enema. There was no statistically significant difference between the 2 groups with respect to age, sex, weight or pre-treatment pain score. The medication was prepared shortly before administration. The enema was always given first and the injection (over 5 min) began immediately afterwards.

Table 1 Reasons for Exclusion of 265 patients

Reason	No. of patients	% of 264
Morphine treatment within 4 h	102	39
NSAID treatment within 24 h	69	26
Informed consent not given	48	18
No clinical symptoms	22	8
Age below 18 or above 75 years	22	8
Peptic ulcer or gastritis	19	7
Severe heart/lung/kidney disease	15	6
Analgesia unnecessary	14	5
NSAID allergy	10	4
Known or suspected pregnancy	4	2
Staff pressed for time	3	1
Already in the study	2	0.8
Haemorrhagic diathesis	1	0.4
Medication lost	1	0.4
Intense pain	1	0.4
Recent surgery	1	0.4
Malignant hypertension	0	0
Not known	1	0.4

Some patients had more than 1 reason for exclusion and not all patients were assessed with regard to all possible reasons.

The intensity of pain was assessed before and 10, 20 and 30 min after administration by a visual analogue scale (VAS, 100 mm). Patients were asked at 30 min whether or not the pain relief was satisfactory; if not, they were given the analgesic commonly used at that particular hospital. All answers were recorded.

Adverse effects were registered on a special form at the time of treatment and a note was made as to whether the complaint was reported spontaneously or elicited by general questioning.

Patients were not allowed to drink liquids while the pain persisted.

Statistical methods

The data were statistically analysed by means of SAS for personal computers (SAS/STAT Guide for Personal Computers, 1987).

The frequency of pain relief (no supplementary analgesia needed) and adverse reactions in the 2 groups were compared by Fisher's exact test (2-sided) in the FREQ procedure.

Within treatment groups, the centres were compared by the 2-sided exact test, for tables with small sample sizes, in the FREQ procedure.

Age, weight and relative pain intensity were compared by Wilcoxon's 2-sample test (2-sided) with respect to treatment groups, and by Kruskal-Wallis's test with respect to the centres within treatment groups. The efficacy of each treatment was tested by a Wilcoxon 1-sample test (null

hypothesis: median relative pain score = 100%) within treatments at 10, 20 and 30 min after each treatment.

Results

After treatment, 17/63 patients in the enema group (27%) needed supplementary analgesia before or 30 min after treatment compared with 5/53 in the intravenous group (9%) ($P=0.018$). The difference between centres within treatment groups was not statistically significant.

The analgesic effect of the 2 treatments was assessed in terms of relative pain intensity, *i.e.* pain intensity as a percentage of initial pain intensity. The mean relative pain intensity as a function of time since treatment is shown in the Figure. Relative pain relief was significantly better in both groups 10, 20 and 30 min after administration than before treatment (all 6 P values $<0.01\%$).

Analgesia was achieved faster in the intravenous group. The difference in relative pain intensity was significant 10 min ($P=0.3\%$) and 20 min ($P=0.2\%$) after administration but not at 30 min ($P=6.3\%$) (Table 2).

Significantly more adverse reactions were reported in the intravenous group (44/80: 55%) than in the enema group (29/79: 37%) ($P=0.03\%$). Most of the reactions were mild or moderate, except for 3 patients in the intravenous group who reported

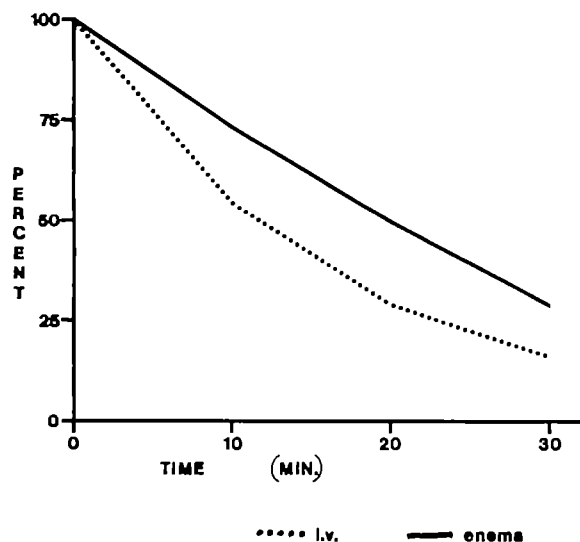


Fig. Mean relative pain intensity. In both groups the difference was significantly better ($P<0.01\%$) 10, 20 and 30 min after treatment than before treatment.

Table 2 Treatment Groups and Response to Indomethacin

Route of administration	Sex	No. of patients	Mean age (years)	Mean weight (kg)	Mean pain score as % of pre-treatment pain score			No. requiring supplementary medication	No. with side effects
					10 min	20 min	30 min		
Intravenous	F	18	45	78	54*	29*	16	5*	44†
	M	35							
Rectal	F	23	47	74	73*	50*	29	17*	29†
	M	40							

*Statistically significant difference between treated groups ($P=0.3\%$).

†Statistically significant difference between treated groups ($P= < 1.8\%$).

severe nausea, vomiting, dyspnoea, a sensation of heat, and tension in the chest. Otherwise the reactions in the intravenous group were mild or moderate nausea, vomiting, giddiness, drowsiness, tiredness, general malaise, or a sensation of heat.

The enema induced defaecation in 5 patients and the need to defaecate in 4. Three patients reported rectal pain/irritation and the rest reported mild nausea, vomiting, a sensation of heat or tingling throughout the body.

Discussion

The intravenous injection of 50 mg indomethacin has proved effective in relieving the pain associated with the passage of a ureteric stone (Holmlund and Sjödin, 1978; Sjödin and Holmlund, 1982; Lehtonen *et al.*, 1983; Udin *et al.*, 1983). This treatment does not have the disadvantages of narcotic analgesics (sedation, risk of dependence and over-treating drug addicts). On the other hand, it does require the presence of medical staff. Rectal administration may be useful in general practice and for self-administration.

In the present study, pain relief in both groups was statistically significant 10, 20 and 30 min after treatment, compared with the intensity of pain before treatment, but significantly more patients in the enema group needed supplementary analgesia after 30 min. An earlier study (Nelson *et al.*, 1988), comparing the effects of indomethacin administered intravenously and rectally, showed no statistical difference in the use of supplementary analgesia 30 min after treatment. The study group was too small, however, for the results to be conclusive.

Thus, although we find the intravenous administration of indomethacin more satisfactory than the enema, the latter still offers advantages to the patient. Adverse reactions were few compared with

those occurring after intravenous injection, and 73% of patients receiving the enema did not need supplementary analgesia. Considering the results reported in other studies after treatment by injection (indomethacin, diclofenac sodium and narcotic analgesics (Holmlund and Sjödin, 1978; Lundstam *et al.*, 1982; Lehtonen *et al.*, 1983; Udin *et al.*, 1983)), this is a high success rate.

In conclusion, most patients with ureteric colic can achieve good pain relief with indomethacin given rectally as an aqueous solution. The side effects are minor when the contraindications are observed.

Acknowledgement

Indomethacin (Confortid) was supplied by Dumex Ltd, Denmark.

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Bladder Calculus Formation as a Complication of the Stamey Procedure

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Summary—Three cases of bladder stone due to a migrated Stamey suture and cuff are reported. In each case peroperative cystoscopy confirmed that the sutures were extravascular. The Stamey cuff subsequently formed a nidus for intravesical stone formation. The mechanism of migration of the cuff, the radiological findings and the operative technique are discussed.

In recent years endoscopic bladder neck suspension, particularly the Stamey technique, has been recognised as safe and effective in the treatment of stress incontinence and the procedure is associated with few significant complications.

None of the major series reviewing the use of the Stamey procedure or any of its modifications has identified bladder stone formation as a complication (Stamey, 1973; Mason and Soderstrom, 1975; Vordermark *et al.*, 1979; Mundy, 1983; Diaz *et al.*, 1984; Fleischer *et al.*, 1984; Gaum *et al.*, 1984; Handley Ashken *et al.*, 1984; Fowler, 1986; Spencer *et al.*, 1987; Jones *et al.*, 1989). Only 2 previous cases have been reported (Zderic *et al.*, 1988; Hargreave, 1988) and in both instances it was suggested that this followed the transvesical positioning of suspension sutures. We report 3 cases of vesical calculi with the “vaginal” cuff as the nidus, following Stamey procedures where peroperative cystoscopy had confirmed the sutures to be extravascular.

Case Reports

Case 1. A 58-year-old woman presented with a 3-month history of haematuria, recurrent cystitis for 12 months and urge incontinence. She also had left loin pain and pyrexia of 40°C.

There was a 20-year history of nephrolithiasis and a parathyroid adenoma had been removed 8 years earlier. She had undergone an abdominal hysterectomy and

Marshal-Marchetti-Krantz procedure 9 years previously and a Stamey procedure for recurrent stress incontinence 2 years previously.

An MSU grew *Escherichia coli* and an IVU demonstrated upper tract obstruction with a calculus at the left vesicoureteric junction. A bladder calculus was present (Fig. 1). Serum calcium was 1.97 mmol/l.

A left nephrostomy tube was inserted and antibiotics commenced. At cystoscopy a vesical calculus was found adherent to the left side of the bladder, the nidus of which was formed by a Stamey suture and cuff. After endoscopic



Fig. 1 Case 1. Post-micturition film. The left ureter is obstructed by a stone at the left vesicoureteric junction and the vesical calculus exhibits the “doughnut” sign due to the pattern of calcification on the dacron cuff forming the nidus. The ribbings of the dacron can also be seen.

litholapaxy the Stamey suture and cuff were removed and Dormia extraction of the left ureteric calculus performed. Review of previous records confirmed that the Stamey suture was extravesical on peroperative cystoscopy.

Case 2. A 69-year-old woman presented with recurrent stress and urge incontinence 1 year after a Stamey procedure. No intravesical suture was seen at peroperative cystoscopy. Radiological investigation revealed a bladder calculus. At cystoscopy a vesical calculus was found adherent to the left side of the bladder superiorly. Endoscopic litholapaxy was performed and the nidus of the stone was found to be a Stamey cuff and suture, which were removed endoscopically.

Case 3. A 78-year-old woman who had undergone a Stamey procedure 14 months previously, followed by a repeat Stamey procedure 2 months later, underwent cystoscopy to investigate persistent symptoms of dysuria, frequency and pain on micturition. Peroperative cystoscopy had shown the Stamey sutures to be extravesical.

A vesical calculus was seen superiorly to the left and the right Stamey suture was found traversing the bladder. Two short suprapubic incisions were made and both superior Stamey cuffs and the sutures were removed. Further inspection of the bladder revealed that the right Stamey suture was successfully removed; litholapaxy of the calculus was performed, the nidus of which was an intravesical Stamey cuff, and this was removed endoscopically.

Discussion

Vesical calculi are uncommon in the female and any history of previous surgery in the region of the bladder must therefore raise the question of an iatrogenic aetiology.

In all of the cases reported here, litholapaxy was easily performed and the cuff was removed by traction. We found the following endoscopic technique particularly convenient in 2 cases, as it avoided the need for open removal of the suture. A urethrotome and a pair of 6 F grasping forceps were introduced separately *per urethram*. The suture loop was visualised through the urethrotome and grasped in the forceps. Traction was applied and the suture divided flush to the bladder wall with the urethrotome. In the third case open removal of the Stamey sutures and cuffs were felt advisable and was performed swiftly and easily via small suprapubic incisions. Endoscopic litholapaxy was required before the left inferior Stamey cuff could be removed endoscopically.

There are only 2 reported cases of bladder calculi forming on the cuff following endoscopic bladder neck suspension. In 1 case the operation notes

could not be found (Zderic *et al.*, 1988) and in the other the bladder was inadvertently transfixated during a Stamey procedure (Hargreave, 1988). The latter is a frequent occurrence during Stamey procedures (Jones *et al.*, 1989), but provided that it is recognised on cystoscopy and the offending suture is repositioned, there are no untoward effects.

It is well recognised that non-absorbable suture material can act as the nidus for stone formation after perivesical surgery (Zderic *et al.*, 1988). However, the question of how a Stamey cuff reaches the bladder, despite endoscopically proven correct placement of the suture, should be addressed, so that amendments to the technique can be made to avoid this complication.

Failure to recognise a transvesical suture may result if only a short length of suture lies in the bladder. It is easy to see how such an unrecognised transvesical suture could pull the Stamey cuff through the tissues and into the bladder. A site where such a suture might be missed is the anterior wall of the bladder; a 120° cystoscope is useful if this area is difficult to visualise. Blood-stained urine emerging from the urethral catheter after insertion of the sutures should also alert the operator to such a possibility. We think that a missed transvesical suture is unlikely in our patients.

Non-absorbable suture material can migrate through the tissues to reach the bladder (Trevino *et al.*, 1979). Therefore, a correctly sited Stamey suture and cuff could migrate into the bladder and act as a nidus for stone formation. If bow-stringing of the suture by the bladder occurs, the suture could erode into the bladder. Subsequent migration of the vaginal cuff through the tissues and into the bladder could then occur as a result of traction. It seems likely that migration of a correctly sited cuff and suture was responsible in our cases. The possibility that the suture was positioned within the thickness of the bladder wall at surgery cannot be excluded. If this was the case, erosion into the bladder would be facilitated. The finding of a cuff within the bladder in all 3 patients indicates that the lower end of the suture must have become dislodged from its position at the bladder neck.

Correct placement of the Stamey suture at the vesical neck, outside the bladder and its wall, is crucial to the success of the Stamey procedure. When careful peroperative cystoscopy has confirmed that the suture is not lying in an intravesical position, additional guidance as to the position of the suture relative to the bladder wall should be obtained by movement of the needle during insertion of a suture as originally described by

Stamey (1973) or by traction on the sutures using a "seesaw" action at the end of the procedure prior to tying the suture. This is the technique we have used. This is important, since a suture lying within the thickness of the bladder wall or in a submucosal position is most likely to erode into the bladder subsequently. Modification of the technique needs to be considered in order to prevent migration of both the Stamey suture and cuff. A factor to be considered is the direction of the traction on the suture; more laterally placed abdominal cuffs would tend to prevent medial migration of suture material into the bladder. An additional modification of the procedure is to use a Raz type suture (Raz, 1981) in combination with the Stamey technique to fix the hitch suture more firmly in the perivesical tissues. Indeed, the observations reported here support the view that if a Raz-type suture alone provides sufficient anchorage, then there is much to be gained in terms of preventing subsequent morbidity by avoiding the use of a lower "buffer" in the future.

The possibility of a vesical calculus should be borne in mind when investigating recurrent urinary symptoms after a Stamey procedure. Although the diagnosis is usually evident from the distinctive "doughnut" pattern of calcification on the tubed material comprising the cuff seen preoperatively on plain radiographs (Fig. 1), all symptomatic patients require cystoscopy to exclude this complication.

Acknowledgements

We thank Mr Handley Ashken for his helpful comments during the preparation of this manuscript. We also thank the Department of Medical Photography, Middlesex Hospital, for their help.

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Computerisation of Urothelial Carcinoma Records: 16 Years' Experience with the TNM System

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Summary—Details of 554 patients with urothelial carcinomas have been recorded on computer forms between 1973 and 1988 inclusive. Essential information from initial assessment and follow-up examinations was printed out on specially designed urothelial update sheets, copies of which were given to patients and urologists as well as being filed in the hospital notes. The survival status of all patients was established as accurately as possible in the last 2 years of the study.

Multivariate analysis of 462 bladder cancer patients with adequate follow-up indicated that T category was the most important discriminating variable, followed by histological grade. After replacing T category by microscopic depth of invasion and bimanual examination, the latter was found to be the most important single variable. The omission of the findings on bimanual examination from the 1987 revision of the TNM classification therefore appears to be wrong.

The long natural history of urothelial neoplasia, together with the many sites and forms in which it occurs and recurs, make computerisation essential for accurate record keeping. For the past 16 years, details of all urothelial tumours have been entered at presentation on specially designed computer forms and data from all follow-up examinations have been similarly recorded (Wickham *et al.*, 1975). At each visit, all of this information was printed out on a "Urothelial Update Sheet" on one side of a piece of A4 paper: one copy was given to the patient and another was attached to the notes, thus facilitating rapid appreciation of the details of each case. During the last 2 years, a data entry clerk was employed to bring all of the information up to date and to establish which patients had died. The data were then subjected to detailed analysis at the Institute of Cancer Research.

The TNM classification of bladder tumours was used throughout, initially with the UICC (1974) T1–T4 system. The division of papillary tumours

into Ta (non-invasive) and T1 (submucosal invasion) introduced in the revised UICC (1978) classification was easily incorporated into the computerised system, since microscopic depth of penetration had been recorded in detail from the start. Recently, certain controversial modifications of the TNM system have been proposed (UICC, 1987; Sobin *et al.*, 1988) which have provoked considerable discussion and the need for these changes has been questioned (Hall *et al.*, 1988; Schroder *et al.*, 1988; Sobin and Hermanek, 1989). In analysing our computerised results, we have accumulated sufficient data to evaluate the established TNM system (UICC, 1974, 1978) and to address some of the questions raised by the modification proposed by the UICC (1987).

Patients and Methods

Between 1973 and 1988 inclusive, 554 new patients with urothelial carcinomas were seen at St Bartholomew's Hospital. Personal details were recorded on the standard green sheet, and findings at initial assessment were entered on a special Urothelial Neoplasia Subcard (yellow sheet); all subsequent

data went on follow-up sheets specially designed for computerisation. The system has been described in detail and illustrated by Wickham *et al.* (1975). In brief, initial assessment included results of intravenous urography, chest X-ray, lymphography and bone scan (if done) and urine cytology; cystoscopic assessment included sites, size, appearance and number of primary tumours, and the findings on bimanual examination under general anaesthesia were recorded. Histological details included cell type, grade of differentiation and depth of invasion in biopsy material. The T classification for bladder tumours was then derived by the computer from this information for each patient and did not change thereafter, as specified in the General Rules of the TNM classification (UICC, 1974).

After initial treatment, follow-up information was obtained either from cystoscopy or out-patient attendance and included results of urine cytology, examination of upper urinary tracts when relevant, and details of any recurrence in bladder or urethra, or evidence of distant metastases. Any additional treatment was recorded. In 1987 and 1988, a research assistant was employed full-time to complete the follow-up information on all patients and to define which patients had died.

Treatment remained fairly constant throughout the period of observation. Superficial papillary tumours were treated endoscopically and followed up with regular cystoscopic surveillance. Intravesical chemotherapy with Epodyl or doxorubicin was used when clinically indicated. Poorly differentiated T1 and all T2 tumours received radical radiotherapy with salvage cystectomy if appropriate for localised recurrence (Hendry, 1986). All T3 tumours were entered into prospective trials, initially comparing pre-operative radiotherapy and elective cystectomy with radical radiotherapy (Bloom *et al.*, 1982) and subsequently with evaluation of adjuvant chemotherapy with methotrexate (Shearer *et al.*, 1988). Patients with T4 tumours and those with metastatic disease received either palliative radiotherapy or chemotherapy.

Survival data were analysed at the Institute of Cancer Research and survival curves calculated by the Kaplan Meier Life Table method (Kaplan and Meier, 1958).

Results

Five hundred tumours were in the bladder, 14 in a bladder diverticulum, 15 extended into the prostatic urethra, while 25 patients presented with upper

Table Age of Patients at Initial Assessment

Age (years)	Number (%)
50	33 (7.1)
50-59	59 (12.8)
60-69	150 (32.5)
70-79	152 (32.9)
80+	68 (14.7)
Total	462 (100.0)
Average (SD)	68.1 (11.6)

tract tumours. Four patients had flat *in situ* carcinoma (TiS), 8 were inadequately assessed and there was 1 papilloma. Of the remaining 487 patients with Ta-T4 bladder tumours, 25 did not attend for follow-up and have been excluded, leaving 462 for detailed analysis. The distribution of the ages of these patients at initial assessment is shown in the Table. Most of the patients were elderly (average age 68.1 years); 355 (76.8%) were men and 107 (23.2%) women; 446 (96.5%) had transitional cell carcinoma, 8 (1.7%) squamous cell carcinoma, 3 (0.6%) pure adenocarcinoma and 5 (1.1%) showed a mixed pattern. Lymphography was done in 24 patients, 12 of whom were positive (NI) and 12 negative (NO). Distant metastases were detected at presentation in 9 patients (1.9%).

A total of 154 patients (33.3%) were known to have died, 282 (60%) were alive on follow-up and 26 (5.6%) had moved away from London. Actuarial survival was calculated from these figures and related to the following characteristics of the 462 Ta-T4 primary bladder tumours.

Size (Fig. 1). There was a significant trend of decreasing survival with increasing tumour size

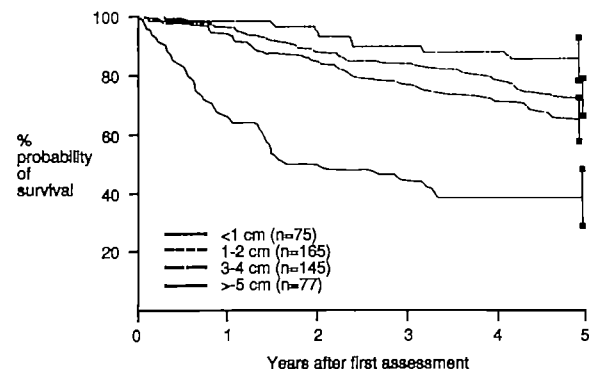


Fig. 1 Survival curves with 95% confidence intervals related to tumour size: 5-year survival rates for tumours less than 1 cm, 85.7%; 1-2 cm, 72.8%; 3-4 cm, 64.9%; 5 cm 39.1%. (Log rank test for trend $\chi^2 = 35.4$; $df = 1$; $P < 0.0001$).

($P < 0.0001$). The 5-year survival rate of patients with tumours of 5 cm or more in diameter was significantly worse than that of patients with smaller tumours ($P < 0.05$), but there were no significant differences between the 5-year survival rates of the other groups.

Number of tumours. Five-year survival rates were 70.5% for 309 patients with single tumours, 55.9% for 45 with single tumours with satellites and 59.6% for 103 with multiple tumours. These rates were not significantly different.

Tumour Appearance (Fig. 2). The 5-year survival rate of patients with papillary tumours (80.1%) was significantly better than that of patients with papillary and solid (49.2%) or solid tumours (36.2%) ($P < 0.05$).

Microscopic Depth of Invasion (Fig. 3). There was a highly significant trend of decreasing survival as the depth of invasion increased ($P < 0.0001$). The 5-year survival rate of patients with invasion of submucosa or beyond was significantly worse than that of those with no invasion ($P < 0.05$).

Bimanual Examination (Fig. 4). There was little difference between the survival curves of patients with soft, freely mobile masses and those with impalpable tumours, the 5-year survival rates being 79.3 and 76.6% respectively. However, it can be seen in Figure 4 that as tumours progressed beyond this stage, survival decreased significantly ($P < 0.0001$). The 5-year survival rate of patients with induration was 48.2%, while that of patients with a hard mobile mass was only 23.3%; all 8

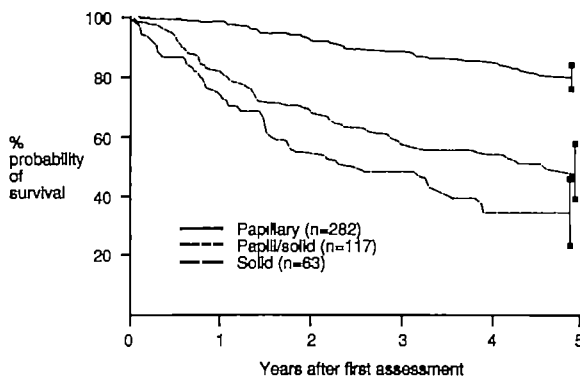


Fig. 2 Survival curves with 95% confidence intervals related to tumour appearance: 5-year survival rates for papillary tumours, 80.0%; for papillary and solid tumours, 49.2%; for solid tumours, 36.2%. (Log rank test for trend $\chi^2 = 66.9$; $df = 1$; $P < 0.0001$).

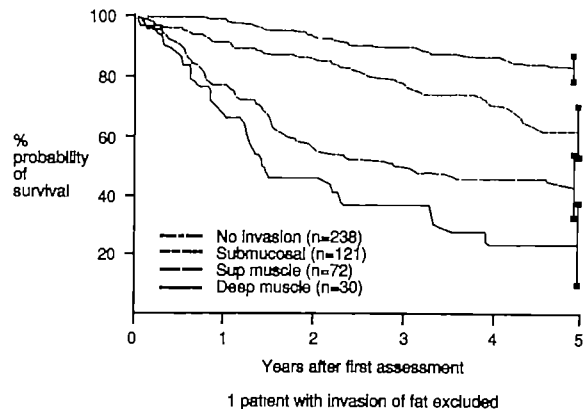


Fig. 3 Survival curves with 95% confidence intervals related to microscopic depth of invasion on biopsy: 5-year survival rates for tumours with no invasion, 81.8%; submucosal invasion, 60.4%; invasion of superficial muscle, 42.1%; deep muscle, 22.6%. (Log rank test for trend $\chi^2 = 73.7$; $df = 1$; $P < 0.0001$). (N.B. 1 patient with invasion of fat excluded).

patients with fixed tumours were dead within 2 years.

T Category (Fig. 5). The 5-year survival rate was significantly better for patients with Ta tumours (83.1%) than for the others ($P < 0.05$). The 5-year survival rates for the other groups were as follows: T1, 67.4%; T2, 52.5%; T3, 33.1%; T4b, 0%. There was a highly significant trend of decreasing survival with increasing T category ($P < 0.0001$).

Grade (Fig. 6). There were clear significant differences in 5-year survival by grade ($P < 0.0001$),

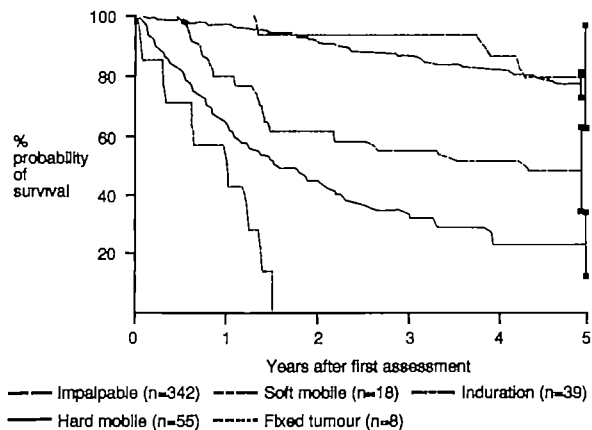


Fig. 4 Survival curves with 95% confidence intervals related to findings on bimanual examination: 5-year survival rates for impalpable tumours, 76.6%; for soft mobile tumours, 79.3%; for those with induration, 48.2%; for hard mobile masses, 23.3%; for fixed tumours, 0%. (Log rank test for trend $\chi^2 = 125.3$; $df = 1$; $P < 0.0001$).

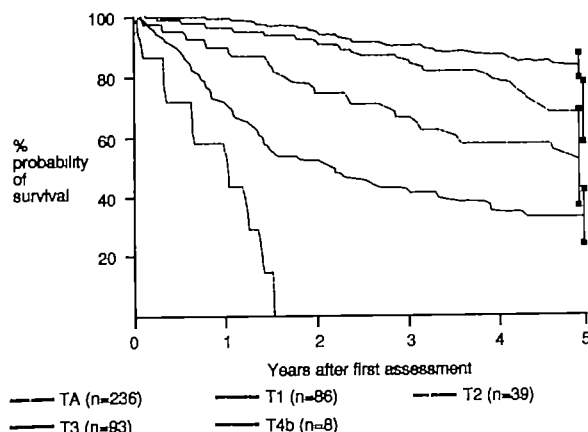


Fig. 5 Survival curves with 95% confidence intervals related to T-category: 5-year survival rates as follows: Ta, 83.1%; T1, 67.4%; T2, 52.5%; T3, 33.1%; T4b, 0%. (Log rank test of trend $\chi^2 = 111.8$; $df = 1$; $P < 0.0001$)

varying from 87.5% for well differentiated (G1) tumours to 66.1% for moderately well (G2) differentiated tumours and 40.0% for poorly differentiated (G3) tumours. Comparison of grade and T classification showed a highly significant correlation between these 2 parameters (Fig. 7). ($\chi^2 = 203.6$; $6df$; $P < 0.0001$).

Since size, grade and appearance of tumour, depth of invasion, bimanual examination and T category were all inter-related in the prediction of likely survival, a multivariate analysis using Cox's proportional hazards model (Cox, 1972) was performed to assess the relative importance of these variables as prognostic factors. However, the T category is a synthesis of microscopic depth of invasion and bimanual examination and, therefore, in order to avoid duplicating these variables, the

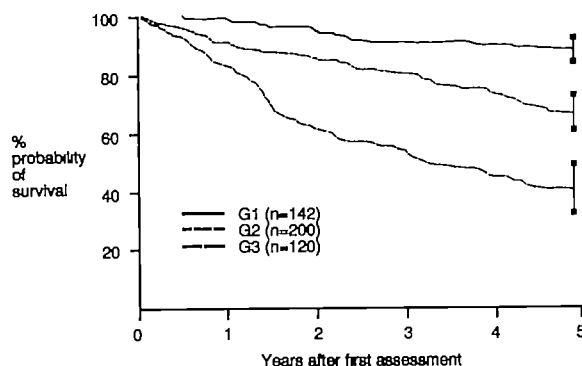


Fig. 6 Survival curves with 95% confidence intervals related to tumour grade: 5-year survival rates as follows: G1, 87.5%; G2, 66.1%; G3, 40.0%. (Log rank test of trend $\chi^2 = 55.6$; $df = 1$; $P < 0.0001$).

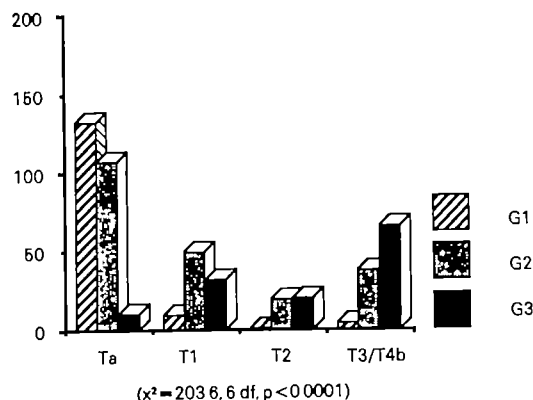


Fig. 7 Relationship between T classification and grade ($\chi^2 = 203.6$; $6df$; $P < 0.0001$).

analysis included size, grade and appearance of tumour and T category only. T category was found to be the most important discriminating variable (likelihood ratio test $P < 0.0001$) and, having fitted this variable, grade was found to be the next most important variable ($P < 0.05$). No other variable contributed significantly to the model. The analysis was re-performed after replacing T category by depth of invasion and bimanual examination. Bimanual examination was found to be the most important variable (likelihood ratio test $P < 0.0001$). Having taken account of bimanual examination, the only other variable which contributed significantly to the model was again grade of tumour ($P < 0.0001$).

Discussion

Computerisation of all cases of urothelial carcinoma offers significant advantages to patients, medical staff and research scientists. From the patient's viewpoint, records are readily available and always up-to-date. By providing each patient with a copy of his or her own computer record and a simple explanation of its meaning, a most valuable partnership is created (Short, 1986), thereby enlisting the patient's aid in ensuring that each check-up is done on time. In our experience almost all patients understood the record sheet and most (70%) felt that patients should have access to their records if computerised, although not necessarily (45%) to their general hospital records. Very few (less than 5%) were worried about keeping a record of their update sheets, although many expressed surprise to learn that they had a serious disease,

having previously understood that they simply suffered from "warts" (Hendry *et al.*, 1988).

Most of the day-to-day value of computerisation of records is lost unless the data can be presented on demand in a readily appreciable "user-friendly" format. The "Urothelial Carcinoma Update Sheet" has proved to be most useful in this respect, summarising the salient features of the initial disease presentation combined with essential details of each subsequent follow-up examination. The interval since the last check on the upper tracts, for example, or an unexpectedly positive urine cytology result after an apparently clear cystoscopy can be instantly appreciated. Furthermore, a change in the behaviour pattern of a particular tumour, sometimes very subtle in clinical presentation, can be appreciated on sequential computer studies and could alert the urologist to the need for more radical therapy.

A welcome product of this research programme has been the ability to carry out not only analyses of individual variables but also a multivariate analysis of patients' survival related to a number of features of their bladder cancers on presentation, without running into problems with too many cells containing small numbers. The results of this analysis show that, although they are significantly associated (Fig. 7), T category and grade are the most important prognostic factors; their importance is clearly illustrated in Figures 5 and 6. These 2 factors can be used to select treatment in some cases—for example, to recommend radiotherapy for T1G3 tumours. However, grading of moderately differentiated tumours, which comprise the majority of bladder tumours, is prone to subjective observer error (Ooms *et al.*, 1983). It is anticipated that computerised nuclear analysis will permit more consistent and accurate assessment of nuclear size and pleomorphism (Jagoe *et al.*, 1984) and thus allow more reliance to be placed on this variable.

Perhaps the most controversial proposal in the 1987 modification of the TNM system of classification of bladder cancers is the omission of the bimanual examination in favour of "imaging", presumably as a result of the advent of sophisticated ultrasound, computed tomography and nuclear magnetic resonance. Our results indicate that of the 2 variables from which the T category (in its 1978 form) is derived, bimanual examination makes the most important contribution to the prediction of likely survival. One may thus conclude that omission of this piece of information is a mistake.

The other variable from which the T category is derived is the depth of penetration of the wall of

the bladder as determined by a representative biopsy. Although depth did not make a significant contribution to the model in the multivariate analysis, it is clear that because T category is the most important prognostic factor, depth of invasion has some role to play in the prediction of likely survival. The marked difference in 5-year survival rates between mucosal tumours and those showing penetration of submucosa provides justification for the distinction between Ta and T1 categories (UICC, 1978) to coincide with the O and A stages of the earlier American classification (Jewett, 1952; Marshall, 1952). The critical relationship between microscopic depth of invasion and survival has been emphasised by Pryor (1973) and more recently by Heney *et al.* (1983), who noted progression in only 4% of patients with Ta tumours compared with 30% of those with T1 growths.

The relationship between grade, muscle invasion and survival is well established (Wallace, 1959). Jewett (1952) recognised the utmost importance of distinguishing pre-operatively between superficially and deeply infiltrating tumours, and from a study of cystectomy cases he suggested that this was best accomplished by the correlation of deep biopsy and bimanual examination under anaesthesia. A palpable mass with sections showing tumour in muscle indicated deep infiltration, whereas if no induration was palpable after transurethral resection the tumour was usually not more than half way through the bladder wall. Recent analysis of a large series of invasive bladder tumours treated by radical cystectomy and pelvic lymphadenectomy (Skinner and Lieskovsky, 1988) suggests that the critical depth of penetration may be into perivesical fat, since the 5-year survival rate fell from 83% (p2) and 69% (p3a) to 29% (p3b)—figures that coincide very well with those derived from the classic autopsy studies of Jewett and Strong (1946), who predicted that 86% of muscle-invasive tumours might be curable, compared with only 20% of those that had penetrated perivesical fat. It may be that the detection of induration or a mobile mass by the relatively crude procedure of bimanual examination under anaesthesia should in fact be considered as presumptive evidence of penetration of the bladder wall into perivesical fat rather than into deep muscle or perivesical fat, as in the present classification.

Analysis of 16 years' experience with computerisation of urothelial cancer records has confirmed the value of this approach to data management in malignant disease. Patients readily understood the importance of keeping their records up-to-date and

this led to improved compliance in follow-up arrangements. The data were presented quickly and efficiently to the medical staff concerned with the patient's care, which saved time and increased efficiency.

Finally, the research scientist was presented with data in a form that was ready for detailed and complex multivariate analysis. This allowed critical re-evaluation and validation of prognostic factors used in the classification of bladder tumours at a time when their relative importance was the subject of review and discussion. It is hoped that the conclusions derived from this study will be of help in forming the next TNM classification and that it will be more acceptable to urologists and oncologists who look after these patients.

Acknowledgements

We thank Mr J. E. A. Wickham for help in originally setting up this computer system and constant encouragement in its early use. We are particularly grateful to Messrs J. P. Ward, D. M. A. Wallace, R. A. Miller and J. W. A. Ramsay, Senior Registrars in the Department of Urology, who organised the patient follow-up and filled in many of the computer forms.

Our thanks also to the Medical Art Department, St Bartholomew's Hospital, for the illustrations, and to Mrs Sally Lisanti, who prepared the typescript.

Financial support was provided by the Cancer Research Fund, St Bartholomew's Hospital, and the Cancer Research Campaign.

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Comparison of Morphometry and DNA Flow Cytometry with Standard Prognostic Factors in Bladder Cancer

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Summary—In 83 bladder cancer patients with adequate follow-up (mean 13 years, range 9–22) the prognostic value of morphometric, DNA flow cytometric and clinical parameters was assessed. Paraffin embedded material was used in flow cytometry. Univariate life-table analysis showed the statistically significant relation of clinical stage, histological grade, mean nuclear area, the Standard Deviation (SD) of nuclear area, mean maximal nuclear diameter, mean nuclear perimeter and the volume corrected mitotic index (M/V index) to survival when bladder cancer deaths alone were used in the analysis. The recurrence of bladder cancer could be predicted with the M/V index. Survival analysis with Cox's regression model pointed to primary tumour clinical stage as the most important prognostic factor of crude survival. Histologically, grade and the SD of nuclear area were the best prognostic factors. Primary tumour stage and histological grade were the best predictors of death from bladder cancer. In Cox's model, histoquantitative methods are almost as good as clinical staging in predicting prognosis. DNA flow cytometry of paraffin embedded material offered no advantage over clinical stage, histological grade or morphology in assessing prognosis.

The prediction of prognosis of human transitional cell bladder cancer can be valuable in selecting patients for different treatments. The value of histopathological grade (Mostofi, 1973; Collan *et al.*, 1979) and clinical stage (Mäkinen *et al.*, 1978; UICC, 1978) is generally accepted. More recently, morphometric methods (De Sanctis *et al.*, 1982, 1987; Goudarzi *et al.*, 1984; Nielsen *et al.*, 1986; Lipponen *et al.*, 1989a), DNA flow cytometry (Hadjissotiriou *et al.*, 1987; Tribukait, 1987; Blomjous *et al.*, 1988; de Vere White *et al.*, 1988; Orntoft *et al.*, 1988; Lipponen *et al.*, 1989c) and the volume corrected mitotic index (Lipponen *et al.*, 1989b) have been used. We decided to compare by multivariate analysis the prognostic relevance of the following parameters in 83 bladder cancer patients: clinical stage (UICC, 1978), histological grade (WHO); volume corrected mitotic index;

mean nuclear area; standard deviation of the nuclear area; mean nuclear perimeter, mean nuclear maximal diameter, mean nuclear form factor, DNA ploidy, S-phase fraction and G2 fraction.

Patients and Methods

The 83 bladder cancer patients in the study were diagnosed and treated between 1965 and 1987 at Kuopio University Central Hospital. They were consecutive bladder cancer (grades I–III) patients for whom complete case histories and histological samples were available. Their age at the time of diagnosis was 67 ± 10 years (range 44–88; male 67 ± 11 years, female 66 ± 6 years). The female: male ratio was 15:68. The mean follow-up time was 13 years (range 9.4–22). The aim of treatment was always curative, so that primary and recurrent tumours were treated as radically as possible. The follow-up and treatment of patients

was done according to standard practice (Gröhn, 1985) and mostly by the same urologist (M.S.). The follow-up investigations were made at 3-monthly intervals during the first 2 years and at 6-monthly intervals thereafter. If a recurrent growth was found, the follow-up programme was started again. Cystoscopy was the method used to detect recurrences in the bladder. The clinical staging of tumours was carried out according to the criteria of UICC (1978).

Histological and morphometric methods

The histological samples were preoperative or transurethral biopsies taken before any treatment was given. The tissue samples were processed according to standard practice and stained with H and E or Van Gieson-iron haematoxylin stains. The histopathological grading of tumours was performed by a specialist histopathologist according to WHO recommendations (Mostofi, 1973). The volume corrected mitotic index, which was determined according to Haapasalo *et al.* (1988) and Lipponen *et al.* (1989c), expresses mitotic activity as the number of mitotic figures/square mm of neoplastic tissue in the microscopic field. In this study 10 fields were counted using a magnification of $\times 40$, which corresponds to about 1 mm² of neoplastic tissue. Counts were started in the most cellular areas and 9 additional (usually consecutive) fields were selected. Only mitotic figures with detectable chromosomes were counted and mitoses were distinguished from pyknotic deformed nuclei by the absence of nuclear membrane and clear central zone, the presence of hairy instead of triangular or spiky projections and basophilic instead of eosinophilic cytoplasm.

In morphometric measurements we used the IBAS 1&2 image analyser in an interactive mode at an objective magnification of $\times 40$. The representative image selected by a specialised histopathologist from the most atypical field of the carcinoma was stored in the computer. One investigator measured the nuclei in the image shown on the monitor with the help of a magnetic digitiser plate. At least 50 nuclei were registered. The mean and standard deviation of nuclear area, mean perimeter, mean longest axis, mean form factor ($4\pi \text{ area}/\text{perimeter}^2$) were calculated. Thus 6 morphometric parameters, histological grade and the M/V index were used in the further study.

DNA flow cytometry

This was performed from paraffin blocks using a

modification of the method described by Hedley *et al.* (1985). Thick sections (50 μm) were used. The pepsin treatment of the deparaffinised sections was replaced by treatment with 10 $\mu\text{g}/\text{ml}$ proteinase K (Sigma) for 30 min at room temperature. After filtration the nuclei were treated with 10 $\mu\text{l}/\text{ml}$ RNase and stained with 25 $\mu\text{g}/\text{ml}$ ethidium bromide (Sigma) for at least 1 h. The DNA was determined with a FACS IV (Becton & Dickinson) instrument using an emission at 488 nm at 200 mW. The total emission above 560 nm was recorded. As the staining intensity of fixed nuclei varied from one sample to another, no internal standard was included. The lowest peak was given a DNA index (DI) value 1 and the DI of other peaks was calculated with this as a reference. Tumours with a DI of 1.00 to 1.049 were recorded as diploid and tumours with a DI > 1.05 were considered aneuploid. The S phase fraction and G2% were calculated using the built-in computer program in the FACS IV. A total of 3 parameters, DI, SPF and G2%, were used in the further analysis. SPF and G2% were determined in 60 of the 83 cases.

Statistical analyses

Three methods were used to evaluate the prognostic value of the parameters.

For each parameter, survival curves (Kaplan-Meier) (Armitage *et al.*, 1988) and recurrence-free intervals were analysed using the SPSS program (SPSS Inc., USA). DI, SPF and G2% were grouped into 2 categories (diploid/aneuploid, SPF below (<6.8%) and above median ($\geq 6.8\%$) and G2% below (<2.6) and above (≥ 2.6) median value. Other quantitative parameters were grouped into 3 categories of approximately the same size (Table 1). A multivariate survival analysis was done using Cox's regression model which takes into account the time at risk from treatment to either death or last follow-up. The third approach was to select 1 time point 5 years after diagnosis and label each patient as dead or alive at that time. This led to 2 patient groups whose corresponding parameters could be studied with respect to their prognostic value with a discriminant analysis. The analysis was done using a stepwise logistic regression. Multivariate survival analyses were done with the BMDP package in a VAX computer (Dixon *et al.*, 1981). The differences between groups were tested using the SPSS program (χ -test, t-test) (Armitage *et al.*, 1988). Definitions for efficiency, sensitivity and specificity were those recommended by Galen *et al.* (1975).

Table 1 Statistically Significant Differences in Crude Survival, Bladder Cancer Survival and Recurrence-free Period between Subclasses of Different Parameters. SD = Standard Deviation, NS = Non-significant

Parameter	Crude survival	Bladder cancer survival*	Recurrence-free period†
Histological grade			
I			
II	NS	$P < 0.001$	NS
III			
Mean of nuclear area (μm)			
<51.5			
51.5–63.0	NS	$P = 0.011$	NS
>63.0			
SD of nuclear area (μm)			
<12.5			
12.5–19.7	NS	$P = 0.001$	NS
>19.7			
M/V index			
<3			
3–18	NS	$P = 0.042$	$P = 0.049$
>18			
TNM classification			
Ta–1			
T2–3	NS	$P = 0.001$	NS
T4			
Lymph node status			
N negative/positive	NS	$P = 0.003$	
Metastasis stage			
M negative/positive	NS	$P = 0.002$	

* Deaths due to bladder cancer only included in the analysis. Mean nuclear maximal diameter ($P = 0.020$), mean nuclear perimeter ($P = 0.023$).

† The time from treatment to first observed recurrence in the bladder.

Results

Univariate life-table analysis

A summary of the significant differences in crude survival (all causes of death included), bladder cancer survival (deaths due to bladder cancer only included) and recurrence-free period (time from treatment to first observed recurrence in the bladder) is shown in Table 1. The clinical stage of the tumour could not predict ($P = 0.11$) crude survival. When bladder cancer deaths alone were included in the analysis the following parameters predicted prognosis in order of importance: clinical stage (Fig. 1), histological grade, the SD of nuclear area (Fig. 2), mean nuclear area and the M/V index. Only the M/V index could predict the recurrence-

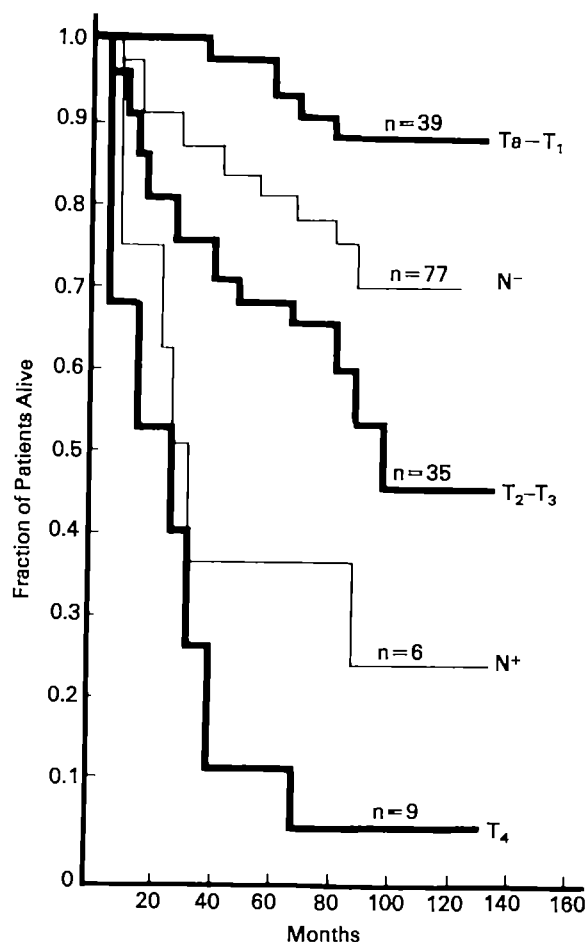


Fig. 1 Survival of patients grouped according to tumour and node stage. The groups and number of cases are shown at the curves. Only cancer deaths are included in the analysis. The differences between the groups are statistically significant (tumour stage groups $\chi^2 = 31.7$, $P < 0.001$, node stage groups $\chi^2 = 9.1$, $P = 0.003$).

free period with statistical significance (Fig. 3). The relation of recurrences to tumour stage did not quite reach statistical significance ($P = 0.08$).

DNA ploidy, SPF and G2% did not have a statistically significant association with crude survival, bladder cancer survival or recurrence-free period (Table 2). DI ($\chi^2 = 6.5$, $P = 0.040$) and SPF ($\chi^2 = 6.1$, $P = 0.047$) were related to histological grade with statistical significance. DI and SPF correlated positively ($\chi^2 = 6.2$, $P = 0.047$). DI ($\chi^2 = 3.3$, $P = 0.19$), SPF ($\chi^2 = 2.1$, $P = 0.343$) and G2% ($\chi^2 = 1.45$, $P = 0.846$) were not related to primary tumour clinical stage. The relationship of DI, SPF and G2% to node involvement and metastasis (Table 3) was not statistically significant.

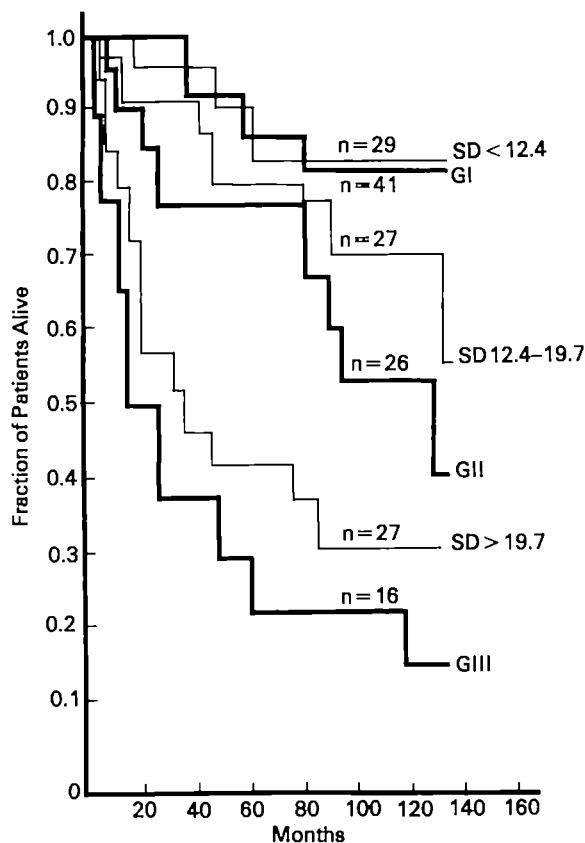


Fig. 2 Survival of patients grouped according to the standard deviation of nuclear area in microscopic images (group limits in μm are shown at the curves) and histological grade. Only cancer deaths are in the analysis. The differences between the groups are statistically significant (the standard deviation of nuclear area $\chi^2 = 17.1$, $P = 0.001$, histological grade $\chi^2 = 26.0$, $P < 0.001$).

Survival analysis with Cox's Regression

The same parameters used in univariate analysis were used in a multivariate survival analysis. A reduction of parameters by stepwise selection and by backward elimination revealed clinical stage as the main predictor of crude survival. However, when histological parameters only were analysed the results pointed to histological grade and the SD of nuclear area as the most important. Bladder cancer survival was related to primary tumour size and to histological grade of the tumour (Fig. 4); node stage was excluded by the analysis as prognostic factors. When the prognostic value of histopathological parameters was analysed, histological grade and SD of nuclear area had statistical significance in that order (Fig. 5). Analysis of the recurrence-free period pointed to primary tumour size as the most important prognostic factor for

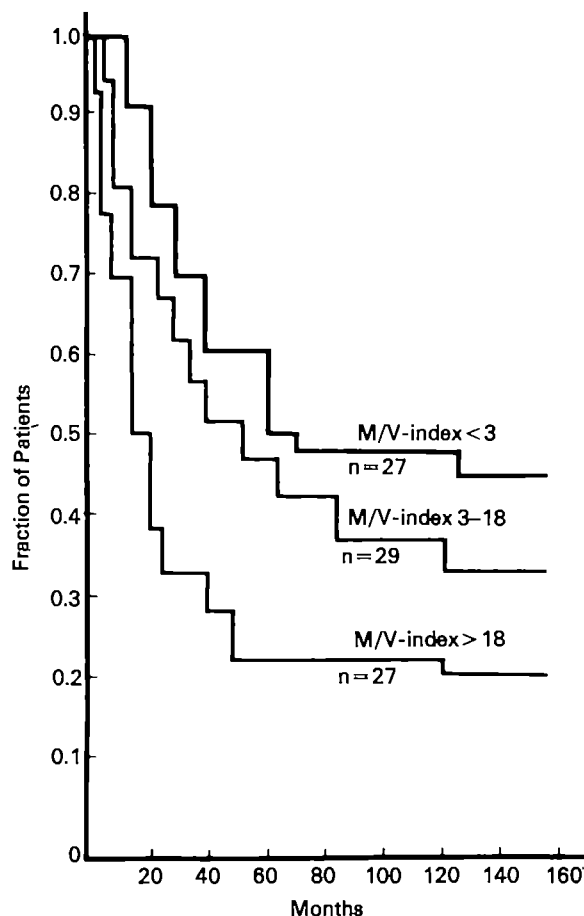


Fig. 3 Relation between volume corrected mitotic index (M/V index) and recurrence-free period. The number of cases and group limits are shown at the curves. The difference between the groups is statistically significant ($\chi^2 = 6.0$, $P = 0.049$).

recurrences (Fig. 6). When histological parameters were analysed separately, grade and SD of nuclear area were the most important and their prognostic score curves were almost identical to those based on tumour size (Fig. 6).

The coefficients and their combined statistical significance in proportional hazards models are shown in Table 4. The prognosticators described above were combined in prognostic indexes or prognostic scores (PS) and are formulated in Table 5.

Discriminant analysis

After a 5-year follow-up, dead (47) and alive (36) patients were compared in a linear discriminant analysis. A stepwise selection showed the same parameter as Cox's model to be the most efficient in predicting crude survival. The probability

Table 2 Relation of DNA Ploidy, SPF and G2% to Mean Survival Time of Bladder Cancer. Patients Dying of Bladder Cancer during the Follow-up Time Alone are included in the Analysis. There is no Statistically Significant Difference in Survival between the Ploidy Groups ($P=0.857$), SPF Groups ($P=0.748$) and G2% ($P=0.08$) Groups. Note that SPF and G2% could be Determined in 60/83 Cases.

	No. of cases	Survival, mean $\pm$ SD, months
DNA ploidy		
diploid	15/83	52.0 $\pm$ 46.8
aneuploid	17/83	49.1 $\pm$ 41.9
S-Phase fraction		
< 6.8	10/60	49.0 $\pm$ 51.4
≥ 6.8	12/60	56.2 $\pm$ 49.6
G2%		
< 2.6	11/60	37.4 $\pm$ 33.1
≥ 2.6	11/60	79.2 $\pm$ 57.5

(counted using prognostic score equation of discriminant analysis for crude survival $PS = -0.734$ (tumour size, TNM) + 1.750) of death within 5 years after diagnosis for patients who died and survived is shown in Figure 7. Using numerical probability 0.5 (a value of the discriminant score) as a decision threshold, the efficiency of the test in making a correct prediction was 0.71, sensitivity 0.50 and specificity 0.87.

Discussion

The most important prognostic factors observed in univariate life-table analyses (Table 1, Figs 1 and 2) are the same as those found in previous studies (Mäkinen *et al.*, 1978; Collan *et al.*, 1979; Goudarzi *et al.*, 1984; Nielsen *et al.*, 1986; De Sanctis *et al.*,

Table 3 The Relation of DNA Ploidy and SPF% to Lymph Node Involvement and Metastasis during the Follow-up Time. Note that SPF could be Determined in 60/83 cases. The P Value of the Difference is shown on the Table.

Metastasis	Diploid*	Aneuploid*	SPF < 6.8†	SPF ≥ 6.8 †
- (56 cases)	28/83	28/83	22/60	19/60
+ (27 cases)	13/83	14/83	9/60	10/60
	$P=1.00$		$P=0.86$	
Lymph node involvement				
- (54 cases)	29/83	25/83	24/60	16/60
+ (29 cases)	13/83	16/83	7/60	13/60
	$P=0.55$		$P=0.11$	

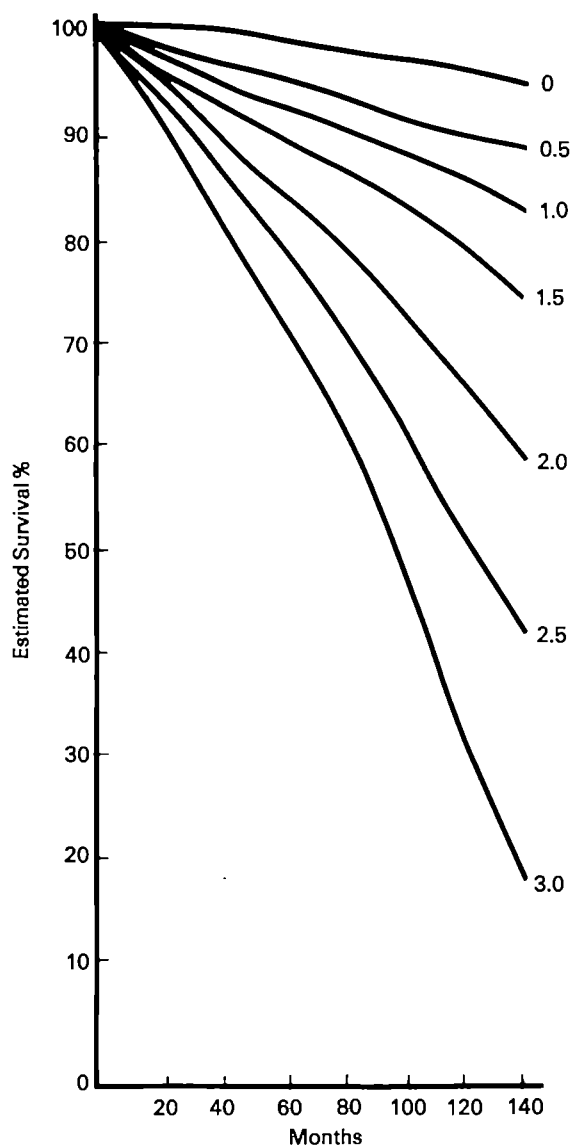


Fig. 4 Bladder cancer survival of patients with different prognostic score values; the prognostic score values are shown at the curves. The equation of prognostic score of bladder cancer survival is 0.506 (tumour size, TNM) + 0.754 (histological grade: 1, 2 or 3); ($\chi^2=41.4$, $P<0.001$).

1987, 1982). The parameters express tumour size, node involvement, metastasis and proliferative activity of bladder epithelium (M/V index), and histology (nuclear area, nuclear area SD and histological grade). Although the results determining DNA ploidy from paraffin blocks are comparable to those of determining it from fresh tissue (Hedley *et al.*, 1985; Nakamura *et al.*, 1987; Jacobsen *et al.*, 1988; Kallioniemi, 1988), we could not demonstrate any prognostic value of DNA

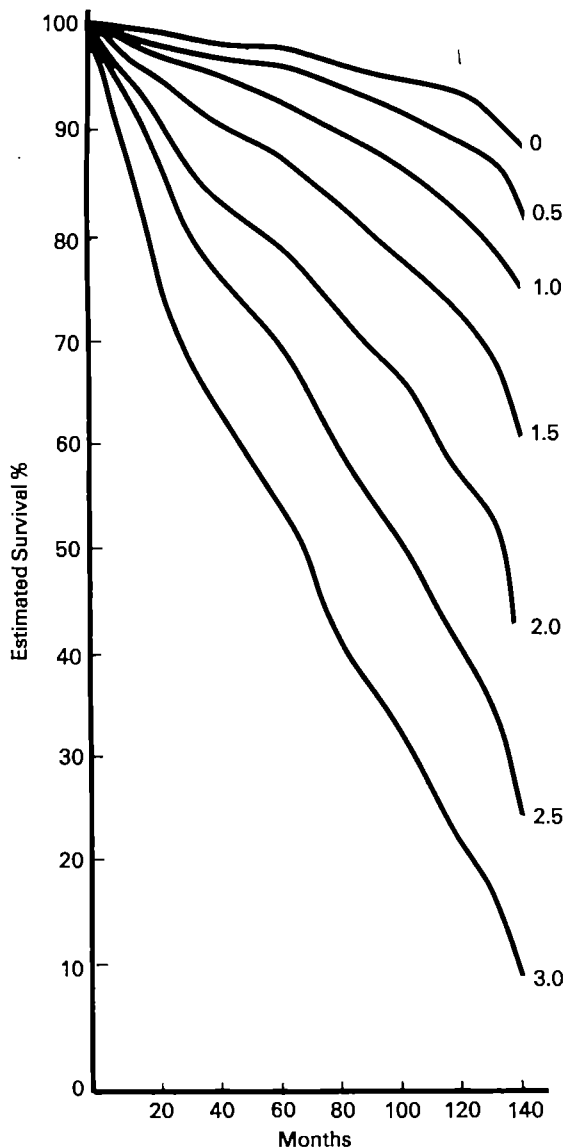


Fig. 5 Bladder cancer survival of patients with different prognostic score values when only histological parameters are included in the analysis; the prognostic score values are shown at the curves. The equation of prognostic score is 0.024 (the SD of nuclear area) $+ 0.973$ (histological grade: 1, 2 or 3); ($\chi^2 = 37.3$, $P < 0.001$).

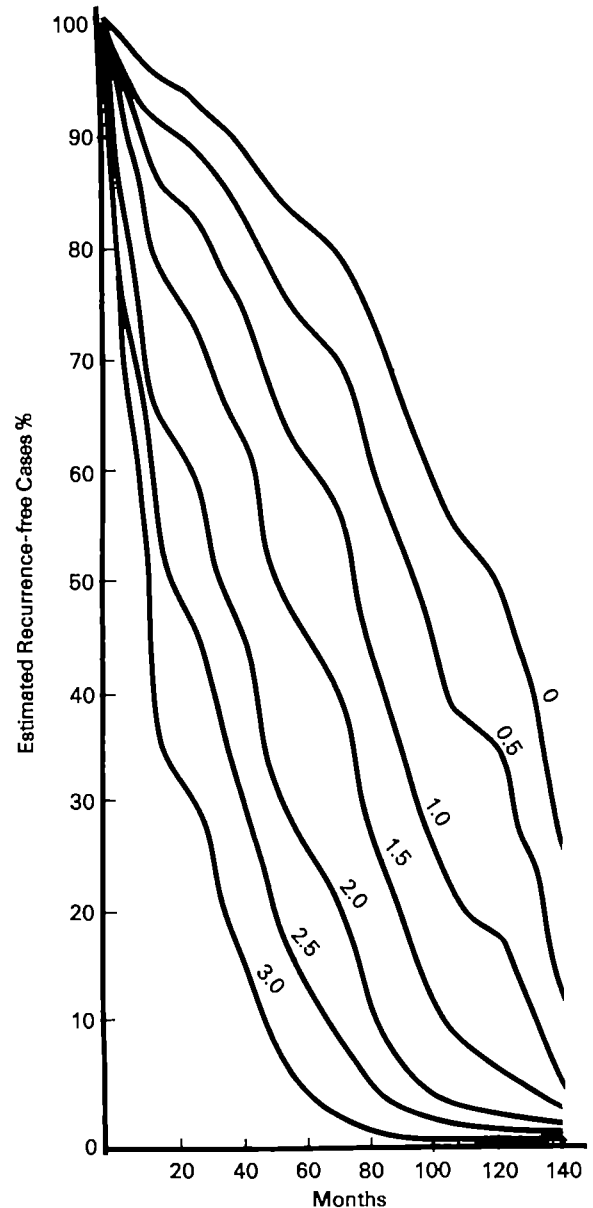


Fig. 6 Recurrence-free period with different prognostic score values according to equation 0.485 (tumour size, TNM).

ploidy. DNA measurements, particularly S-phase determinations, from paraffin blocks are subject to many variations, *e.g.* intratumour heterogeneity (Kallioniemi, 1988), and admixture of non-tumour cells (Jacobsen *et al.*, 1988), that a statistically significant association with long-term prognosis cannot be achieved (Lipponen *et al.*, 1989c). In our analysis, as observed earlier (Ooms *et al.*, 1985;

Lipponen *et al.*, 1989a), we demonstrated that histological grading adds little to the morphometric grading of bladder tumours. In agreement with earlier findings (Goudarzi *et al.*, 1984; Nielsen *et al.*, 1986; De Sanctis *et al.*, 1987, 1982; Lipponen *et al.*, 1989a), patients with a larger mean and standard deviation of nuclear area values have a worse prognosis. Morphometric measurements are more

Table 4 Coefficients of the Proportional Hazards Model of the Most Important Prognostic Parameters. χ^2 (Chi Square-Test Value) and *P* (probability) express Statistical Significance of the Combination of Parameters. T = Tumour Size, M = Metastasis Stage (TNM) at the Time of Diagnosis. SD = Standard Deviation, SE = Standard Error, Coef. = Coefficient.

Analysis	Coef.	Coef./SE	χ^2	<i>P</i>
Crude survival				
T	0.498	4.255	51.9	<0.001
M	2.925	3.338		
Crude survival, histology				
Nuclear area SD	0.022	2.132	17.9	<0.001
Histological grade	0.474	2.344		
Bladder cancer survival				
T	0.506	3.455	41.45	<0.001
Histological grade	0.754	2.832		
Bladder cancer survival, histology				
Nuclear area SD	0.024	2.177	33.7	<0.001
Histological grade	0.973	3.675		
Recurrence-free period				
T	0.485	3.489	13.1	<0.001
Recurrence-free period, histology				
Nuclear area SD	0.023	1.923	13.3	<0.001
Histological grade	0.523	2.100		

reproducible than histological grading by a pathologist (Ooms *et al.*, 1983), are simple, and can be done routinely in most pathology laboratories.

The recurrence of bladder tumours (Table 1, Fig. 3) was related to the M/V index in univariate analysis. Of the histological parameters in Cox's

Table 5 Prognostic Scores (PS) of Crude Survival (All Causes of Death Included in the Analysis), Bladder Cancer Survival (Deaths due to Bladder Cancer Only Included in the Analysis) and Recurrence-free Period (Time from Radical Treatment to First Observed Recurrence in the Bladder).

Crude survival
PS = 0.498 (tumour size, TNM) + 2.925 (metastasis stage, 0 or 1)
PS (histology only included) = 0.022 (nuclear area SD, μm) + 0.474 (histological grade: 1, 2 or 3)
Bladder cancer survival
PS = 0.506 (tumour size, TNM) + 0.754 (histological grade: 1, 2, or 3)
PS (histology only included) = 0.024 (nuclear area SD, μm) + 0.973 (histological grade: 1, 2 or 3)
Recurrence-free period
PS = 0.485 (tumour size, TNM)
PS (histology only included) = 0.023 (nuclear area SD, μm) + 0.523 (histological grade: 1, 2 or 3).

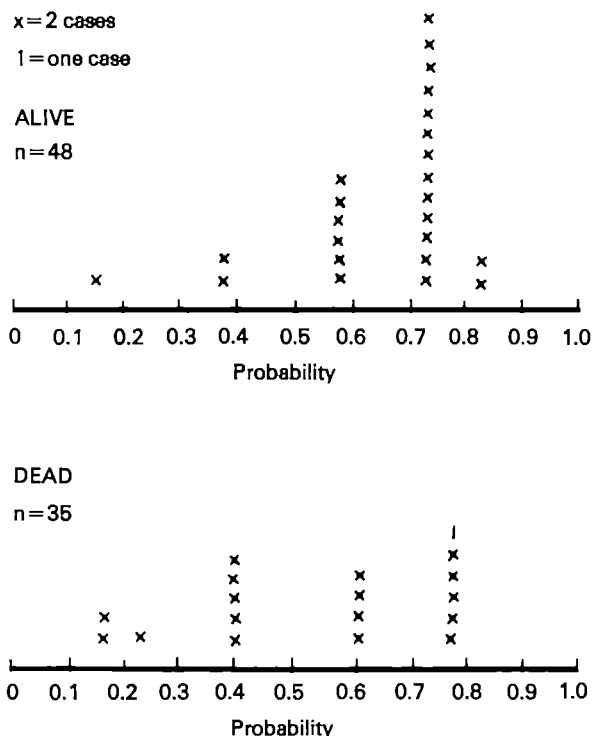


Fig. 7 Results of discriminant analysis. Numeric probability of death within 5 years after diagnosis.

model, the SD of nuclear area and histological grade were most efficient predictors of recurrence-free period (Tables 4 and 5). However, multivariate analysis revealed primary tumour stage as the most important parameter (Fig. 6). Mitotic activity and nuclear area SD have been reported to be related to recurrences in breast cancer (Stenqvist *et al.*, 1982). Although a significant prognostic factor in univariate analysis, the M/V index is not included in the Cox's model. Cox's model in principle is based on a theoretical model which takes into account the time at risk from treatment to first observed recurrence. Differences in follow-up time may thus cause discrepancies in the results between univariate analysis and Cox's model.

Multivariate prognostic scores and numerical probabilities have been applied successfully in predicting cancer behaviour (Gamel *et al.*, 1982; Stenqvist *et al.*, 1982; Baak *et al.*, 1985; Montironi *et al.*, 1986; Chevalier *et al.*, 1988; Collan *et al.*, 1988; Haapasalo *et al.*, 1989). The crude survival and recurrence of bladder cancer in our series was related to clinical stage (Tables 4 and 5) in Cox's analysis. This finding can easily be understood since a large tumour with metastasis has a poor

prognosis. The relatively low sensitivity of the test in discriminant analysis is easy to understand since most deaths in this elderly population are due to diseases other than bladder cancer. Most patients in this study were male smokers (65%) who were at an increased risk of cardiovascular and respiratory diseases. Node involvement had no predictive value. When histological parameters alone were analysed, nuclear area SD and histological grade predicted survival well. The prediction capacity of morphometry makes it a valuable tool in grading and defining prognosis in bladder cancer. Histological grading, although subjective, also added significantly to the predictive power of the analysis.

In this series, the prognostic power of the SD of nuclear area was approximately the same as that of node stage in univariate analysis. Histological grade predicted survival as well as clinical stage at the time of diagnosis (Figs 1 and 2). In multivariate analysis, when crude survival was analysed, clinical stage was the best predictor of survival. When bladder cancer deaths and recurrences were analysed, histoquantitative methods were as good as clinical staging. When the primary clinical stage is not known, histoquantitative methods offer a reliable method of evaluating prognosis with a relatively small method variation (Ooms *et al.*, 1983; Ooms *et al.*, 1985; Collan *et al.*, 1987; Lipponen *et al.*, 1989d).

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Intraprostatic Antibody Deposition in Chronic Abacterial Prostatitis

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Summary—Sixty patients with chronic abacterial prostatitis and 21 men without prostatitis were studied. Transperineal prostatic biopsies taken under transrectal ultrasound control were examined for antibody, complement (C₃) and fibrinogen deposition using a direct immunofluorescence (IF) technique; 34 patients (57%) had prostatic tissue that displayed IF staining compared with only 1 (5%) in the non-prostatitis group. IF staining for IgM was found in 85%, for C₃ in 44%, for IgA in 35% and for fibrinogen in 24%, but the IgG subclass was not detected. Antibody deposition was mainly periglandular and glandular and in the wall of vessels. Five symptoms, particularly poor urinary flow, irritative voiding and urgency, were significantly correlated with IgM and C₃ deposition and, to a lesser extent, fibrinogen deposition. The aetiology of chronic abacterial prostatitis remains obscure but several possible mechanisms are discussed. The link between symptomatology and immunology could rest with functional outflow obstruction causing intraprostatic reflux of urine, this in turn inciting an immunological response, the inducing antigens being organism remnants or products, urinary constituents or autoantibodies.

The aetiology of chronic abacterial prostatitis as defined by Drach *et al.* (1978) remains obscure. A number of micro-organisms have been suggested as a cause, including *Chlamydia trachomatis* (Mårdh *et al.*, 1972, 1978; Poletti *et al.*, 1985) and *Ureaplasma urealyticum* (Brunner *et al.*, 1983). Equally, others have failed to locate these or any other organisms in prostatic secretion or tissue of patients with chronic abacterial prostatitis (Doble *et al.*, 1989a,b).

Studies of the immunological background of prostatitis have been directed mainly at the chronic bacterial form where elevated levels of immunoglobulin have been found in both the prostatic fluid and serum (Gray *et al.*, 1974; Shortliffe *et al.*, 1981; Fowler *et al.*, 1982). A similar pattern has been shown in abacterial prostatitis (Shortliffe and Wehner, 1986) but levels of immunoglobulin were lower than those seen in chronic bacterial prostatitis

and lacked antigen specificity for the *Enterobacteriaceae*. Local prostatic immunoglobulin of the IgG and IgA classes has also been detected in normal glands, obtained at necropsy, by Ablin *et al.* (1971) using a direct immunofluorescence technique.

In patients with interstitial cystitis, immunoglobulin deposits have been noted within the bladder (Gordon *et al.*, 1973; Mattila, 1982) and are felt to be involved directly in the pathogenesis of this condition. Similarly, several dermatological (Harrist and Mihm, 1979) and renal (Albini *et al.*, 1979) conditions have been characterised by immunoglobulin deposition. These observations have stimulated a search for intraprostatic immunoglobulin deposition in patients with chronic abacterial prostatitis in an attempt to define its pathogenesis and possibly to further characterise this disease.

Patients and Methods

Patients attending the sexually transmitted diseases and urology clinics at St Mary's Hospital with a

clinical diagnosis of prostatitis were studied. All underwent the Stamey procedure (Meares and Stamey, 1968) and 60 of them, ranging in age from 19 to 75 years (mean 40.2), were diagnosed as having abacterial prostatitis. The diagnosis was made if there were (1) ≥ 10 leucocytes/high power microscope field ($\times 1000$) on examination of expressed prostatic secretion (EPS), providing there were fewer leucocytes in urethral (VB1) and bladder (VB2) urine samples and/or (2) ≥ 5 leucocytes/high power field ($\times 400$) in the post-prostatic massage urine (VB3) and (3) bacterial, chlamydial or mycoplasmal infections could not be diagnosed according to criteria presented previously (Doble *et al.*, 1989a, b). In addition, 21 patients aged 20 to 68 years (mean 39.2) without prostatitis were studied as controls.

After the Stamey procedure each patient underwent transrectal prostatic ultrasound using a Bruel and Kjaer 1846 ultrasound machine with a 5.5 MHz transducer. The examination was performed in the left lateral position and the findings recorded on X-ray plate.

A transperineal prostatic biopsy was undertaken on all patients after obtaining written consent. The procedure was performed initially in the lithotomy position but later in the study in the left lateral position under light sedation induced by intravenous Diazemuls and local perineal anaesthesia (1% lignocaine). The biopsy was taken with a 14 g Tru-cut (Travenol) needle inserted under ultrasound control into the abnormal area of the prostate. The tissue obtained was subdivided, one portion being placed immediately into formol saline for routine histological examination and the remainder into transport medium for subsequent study by immunofluorescence. The transport medium consisted of 3.12M $(\text{NH}_4)_2\text{SO}_4$, 0.005M N-ethylmaleimide, 0.005M MgSO_4 and 0.025M potassium citrate, pH 7.0–7.2.

The specimen was removed from the transport medium and washed in running water for 10 min before being embedded in OCT (Miles Scientific Laboratory Ltd) and frozen in isopentane, pre-cooled in a bath of liquid nitrogen, and stored in liquid nitrogen. Cryostat sections, 6 μm thick, were cut at -25°C and allowed to air dry. Then they were washed for 30 min in 0.15M phosphate buffered saline (PBS), pH 7.2, and air dried prior to applying the fluorescein-conjugated polyclonal rabbit anti-human antibodies to IgM, IgG, IgA, C3 and fibrinogen (Dakopatts). The IgG antibody was diluted 1:100 and all other antibodies 1:50 and applied to the section for 30 min. After a further

wash in PBS for 30 min the section was counter-stained with Evans blue and mounted in PBS and glycerol. The slides were examined by fluorescence microscopy for the presence of antibody, complement and fibrinogen and the class of antibody and its deposition site were noted.

The results were analysed by means of a univariate system in which an assessment was made of how age, symptoms and their duration, and histological features correlated with immunofluorescence.

Results

All of the 60 patients had evidence of prostatitis based on the Stamey localisation procedure. In 18 patients the diagnosis was made on the presence of leucocytes in EPS and VB3 samples and in the remaining 42 on leucocytes in the VB3 sample alone. None of the 21 controls had either cytological or microbiological evidence of prostatitis as judged by the Stamey procedure.

The areas of abnormal echogenicity on prostatic ultrasound, namely high and mid-range density echoes and hypoechoic zones, were biopsied. In 53 patients (88%), the presence of prostatitis indicated by the Stamey procedure was confirmed by histological examination of the prostatic tissue. In 2 patients the tissue was normal and in 5 insufficient tissue for diagnosis was obtained. The majority displayed a low grade chronic inflammatory infiltrate on histological analysis (Table 1). Lymphocytic infiltration was graded on a scale of 1 to 3,

Table 1 Histological Features of Prostatic Biopsies

Feature	No. of patients (%)
<i>Inflammatory cells</i>	
Acute and chronic	5 (8)
Chronic: grade 1	38 (63)
grade 2	9 (15)
grade 3	5 (8)
Granulomatous*	1 (2)
<i>Site of inflammation</i>	
Intraglandular	7 (12)
Periglandular	40 (67)
Stromal	27 (45)
Fibrosis	19 (32)
Vessel hyaline thickening	14 (23)

**Mycobacterium tuberculosis* excluded.

grade 1 being 5–10 cells/high power field (hpf), 2 being 11–15 cells/hpf and 3 being more than 15 cells/hpf. The lymphocytes were most often located in the periglandular and stromal regions and were rarely intraglandular. Fibrosis was found in 32% of biopsies and vessel thickening in 23%. Of the 21 control biopsies, 16 were normal, 4 showed benign prostatic hyperplasia and in 1 an unexpected carcinoma was found. All controls were graded as normal with respect to the presence of a chronic inflammatory infiltrate, *i.e.* there were less than 5 inflammatory cells/hpf.

Thirty-four patients (57%) had prostatic tissue that exhibited immunofluorescence staining, indicating the presence of immunoglobulin, complement or fibrinogen, compared with 1 (5%) of the controls ($P < 0.001$). In particular, the patient with granulomatous prostatitis had no antibody deposition. Amongst the patients who showed immunofluorescence staining of prostatic tissue, IgM (Figs 1 and 2) was detected in 29 (85%), C₃ (Fig. 3) in 15 (44%), IgA (Fig. 4) in 12 (35%) and fibrinogen in 8 (24%). The IgG subclass was not detected. The patient with prostatic carcinoma exhibited IgM and IgA deposition. The sites of antibody deposition are detailed in Table 2, periglandular, glandular and vessel deposition being the most prevalent.

The relation between age, symptoms and histological features on the one hand and immunofluorescence on the other was analysed and the results are summarised in Table 3. Several symptoms were significantly correlated with IgM and C₃ deposition and, to a lesser extent, with fibrinogen deposition. There was no correlation, however, between age, symptom duration, inflammatory grade and site, and positive immunofluorescence. The only correlation between histological features and the immunofluorescence findings was a significant association between vessel thickening and positive immunofluorescence ($P < 0.05$).

Table 2 Site of Antibody, Complement and Fibrinogen Deposition

Site	% of patients with prostatic immunofluorescence-staining
Periglandular tissue	79
Gland	62
Vessel wall	62
Luminal cells	41
Luminal surface	21
Stroma	29

Table 3 Significant Correlations between Symptoms and Immunofluorescence Findings

Symptoms	Findings	P
Poor urinary flow	Immunofluorescence positivity	<0.01
	IgM deposition	<0.01
	IgM deposition in luminal cells	<0.02
	C ₃ deposition	<0.01
Irritative voiding	IgM deposition in stroma	<0.01
Urgency	IgM deposition in luminal cells	<0.01
Frequency	Fibrinogen deposition	<0.05
Nocturia	IF positivity	<0.05
Testicular pain	IF positivity	<0.05
History of NGU	C ₃ deposition	<0.02

Discussion

The finding of IgM and IgA antibodies, complement and fibrinogen deposition within the prostate of chronic abacterial prostatitis patients, but not controls, suggests that these antibodies are not those normally secreted by the prostate gland but are formed in response to an extrinsic antigen. These results contrast with those of a study of normal cadaveric prostate and benign prostatic hyperplastic tissue (Ablin *et al.*, 1971) where IgG and IgA were found in granules within the ductal lumen, IgG in the basal portion of the prostatic acini and IgA in the stroma. It was concluded that these antibodies were part of the normal secretion of the prostate. The discrepancy between these results and our findings is difficult to explain, particularly as the method of production of the goat anti-human antibody in the former study (Ablin *et al.*, 1971) was not described. The antigens used to stimulate the rabbit anti-human antibodies in our study were IgG, IgM, IgA and C₃ pooled from human serum and fibrinogen from pooled plasma. The IgA fraction in our study was not of the secretory type which accounts for most of the IgA normally secreted by the prostate (Fowler and Mariano, 1984), but the absence of the IgG suggests that the antibodies used in our study were of different specificity from those used by Ablin *et al.* (1971).

A similar panel of antisera to those adopted in our work was used by Vinje *et al.* (1983) to examine frozen sections of prostatic tissue from patients with chronic prostatitis. In most biopsies a diffuse extracellular fluorescence was detected, indicating the presence of IgA, IgG and IgM; some biopsies possessed immunoglobulin-containing cells, but complement was not detected and all biopsies stained weakly positive for fibrinogen. The authors

were loath to draw firm conclusions, save that the immunoglobulin present had probably diffused passively from the serum. The diagnosis of prostatitis in this study based on symptoms, signs and the finding of ≥ 10 leucocytes/hpf in the EPS, rather than the Stamey localisation method (Meares and Stamey, 1968), together with the adoption of a blind prostatic biopsy technique and failure to analyse prostatic tissue from normal controls, certainly throws doubt on the significance of the findings.

Since the finding of antibody-coated bacteria in the urine of patients with chronic bacterial prostatitis (Jones, 1974) there has been increased interest in the immunoglobulins within prostatic fluid, described previously in normal subjects (Chodirker and Tomasi, 1963). In a group of patients with a diagnosis of prostatitis, though localisation studies were not detailed, significantly increased levels of IgG, IgM and IgA were found within the EPS compared with controls (Gray *et al.*, 1974). It has also been noted that immunoglobulin levels, in particular IgG and IgA, were greater in chronic bacterial prostatitis than in chronic abacterial prostatitis and remained elevated in cases that failed to resolve, yet returned to normal in those that responded satisfactorily to treatment (Fowler and Mariano, 1984; Shortliffe and Wehner, 1986). In another study (Shimamura, 1979), levels of IgM, in addition to IgG, in EPS were found to follow a similar pattern.

The total and organism-specific immunoglobulin levels in EPS have now been measured by several investigations (Shortliffe *et al.*, 1981; Fowler *et al.*, 1982; Wishnow *et al.*, 1982; Fowler and Mariano, 1984; Shortliffe and Wehner, 1986) and the general consensus is that the levels of IgG and IgA in prostatitis are elevated compared with those in controls. The IgA response was most marked and represented production within the prostate rather than transudation from the serum. The elevated levels of these immunoglobulins in chronic abacterial prostatitis were less than those in chronic bacterial prostatitis and were not specific for the *Enterobacteriaceae* (Shortliffe and Wehner, 1986). Thus chronic abacterial prostatitis does not appear to be an occult infection by these organisms that has escaped detection. Interestingly, elevated IgM levels in EPS were not detected in these later studies. This contrasts with the earlier ones (Gray *et al.*, 1974; Shimamura, 1979) and with our study in which this immunoglobulin class was the most prevalent. However, it is possible that we are dealing with different types of immunoglobulin,

since those detected in our study were tissue bound rather than free within the prostatic secretion.

Interstitial cystitis has been studied by 2 groups of investigators (Gordon *et al.*, 1973; Mattila, 1982) seeking evidence of immunoglobulins and complement within the tissues. IgM featured in both studies and in 1 (Mattila, 1982) it was detected, along with C₃, in the vessel walls of the bladder. IgM was postulated either to be part of a circulating immune complex or produced in response to an exposed antigen within the vessel wall which subsequently triggered the complement cascade (Mattila, 1982). Our results are similar, with IgM (85%) and C₃ (45%) being found most often and, although the preferred site was the periglandular region, vessel wall deposition was also prominent. The predominance of IgM in a chronic condition is curious but may reflect repeated secretion in response to a new antigen, a viral aetiology or possibly an autoimmune process. Vessel wall deposition of immunoglobulin together with complement may imply the existence of circulating immune complexes.

The majority of symptoms that showed a significant correlation with immunofluorescence staining were concerned with voiding dysfunction and irritative voiding. Poor flow correlated with immunofluorescence positivity in general, but with IgM and C₃ deposition and IgM deposition in the luminal cells in particular. It is difficult to ascertain whether irritative voiding results in immunofluorescence positivity or whether prostatic inflammation exerts an irritative effect on the trigone. In a study of 50 patients with symptoms of prostatitis, 52% had a sensory problem on urodynamic testing and 46% had detrusor instability (Murnaghan and Millard, 1984). Such abnormalities may be present in our patients, though none has undergone urodynamic assessment. On the other hand, the link between symptomatology and immunology may rest with functional outflow obstruction such as occurs in incomplete relaxation of the distal sphincter (Buck, 1975; Hellstrom *et al.*, 1987) where high pressure within the prostatic urethra is produced during voiding with resultant intraprostatic reflux of urine (Kirby *et al.*, 1982). The urine within the prostatic ducts and acini may then incite an immunological response, either by acting as a carrier of antigen or possibly through its chemical properties. The presence of IgM in the luminal cells may indicate an intracanalicular route for the inducing antigen. Significant C₃ deposition was linked with a history of non-gonococcal urethritis, which may indicate that causative organisms of



Fig. 1 Surface and glandular IgM deposition.

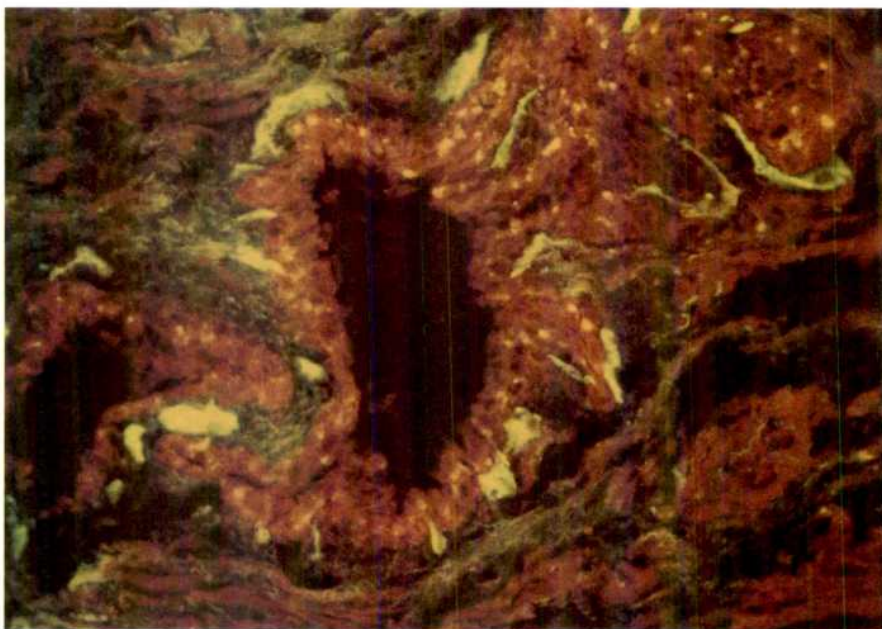


Fig. 2 Basal glandular and periglandular IgM.

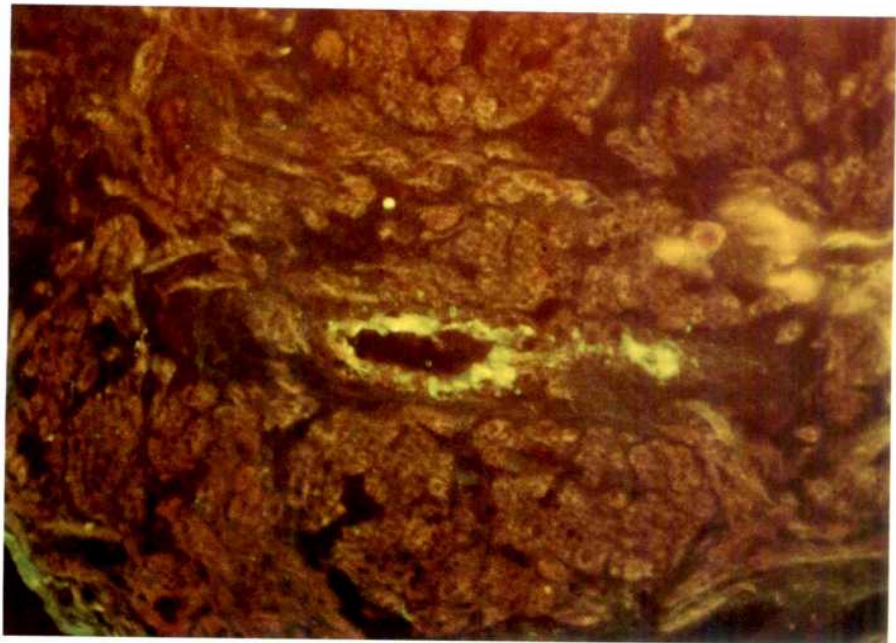


Fig. 3 C₃ deposition in vessel wall.

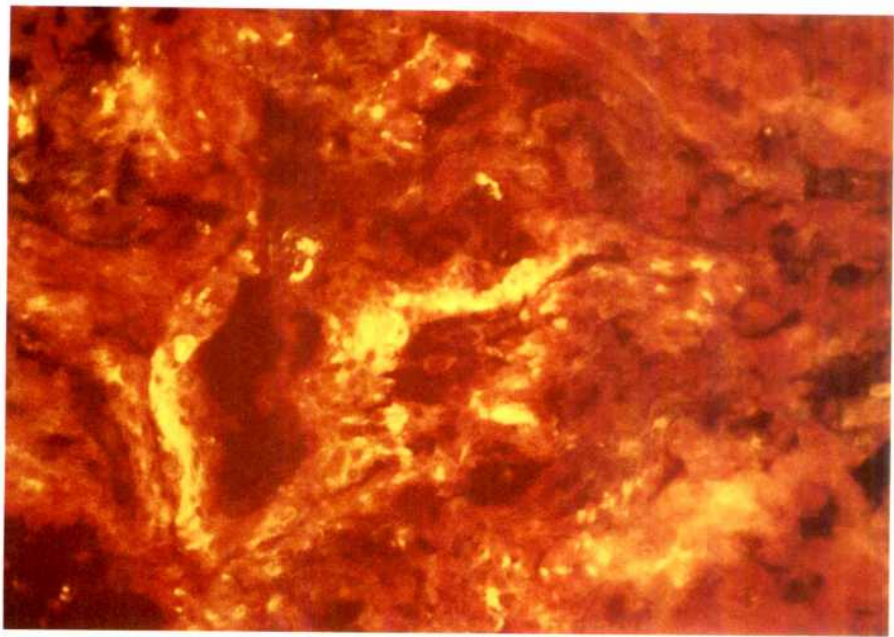


Fig. 4 Intraglandular IgA deposition.

this condition, i.e. *Chlamydia trachomatis* and *Ureaplasma urealyticum*, which spread intracanalicularly, are implicated in chronic abacterial prostatitis. If the immunoglobulin and complement deposition reflect antibody formed in response to these organisms, then it would be to non-viable antigens that remain bound to the tissues, since we have been unable to find an active role for them in this condition (Doble *et al.*, 1989a, b).

The absence of any correlation between the severity of inflammation and immunofluorescence positivity in our patients is at variance with the results of a similar study of the painful bladder syndrome (Witherow *et al.*, 1989) but suggests that the inflammatory response is not an entirely antibody driven process. It would be of interest to determine the relationship of B cells to these immunoglobulin deposits in order to ascertain if they were being actively secreted and if the prostate was indeed the site of their production. The significant correlation of vessel thickening with immunofluorescence positivity ($P < 0.05$) and the deposition of C₃ within vessels imply that a proportion of these immunoglobulins are circulating immune complexes.

Most of our patients (57%) had immunoglobulin, complement and fibrinogen deposition within the prostate but there was no clear relationship between immunofluorescence staining and aetiology, save possibly voiding dysfunction in the form of poor urinary flow. It remains to be seen whether the subgroup with immunofluorescence staining represents a truly different category in terms of disease natural history and response to treatment. This information can be gained only by longitudinal studies, possibly including follow-up prostatic biopsy.

Although the aetiology of chronic abacterial prostatitis remains obscure, the identification of intraprostatic immunoglobulin, complement and fibrinogen is a stimulus to search for the inducing antigens. Possible candidates would appear to be organism remnants or products, urinary constituents and autoantibodies. It is hoped that this shortlist can be reduced by further immunological studies currently in progress.

Acknowledgement

We are grateful to Dako Ltd for their help in sponsoring the cost of the colour prints used in this publication.

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Inflammatory Infiltrate in Prostatic Hyperplasia—Evidence of a Host Response to Intraprostatic Spermatozoa?

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Summary—The inflammatory infiltrate was characterised in 20 samples of prostatic hyperplasia using cell surface specific monoclonal antibodies. The infiltrate was composed predominantly of CD-3+ T-lymphocytes. The distribution of the T-lymphocyte subsets (CD-4 and CD-8) between the epithelial and stromal components of the gland was significantly different, with most of the intra-epithelial infiltrate being CD8+, T cytotoxic/suppressor cells. This may be a necessary immunological barrier, as in the epididymis, to prevent the development of autoimmunisation to sperm antigens.

Large numbers of CD4+ T helper/inducer cells and significant numbers of CD-11c+ macrophages were demonstrated in the extra-glandular stromal tissues, suggesting a delayed type hypersensitivity reaction.

Intraprostatic spermatozoa have been demonstrated recently and we have confirmed this finding on post mortem specimens. It is postulated that the presence of an intra-epithelial cytotoxic barrier and the marked stromal infiltrate may be due, in part, to the intermittent presence of spermatozoa within the prostate.

It is well documented that there is an “inflammatory” infiltrate in the majority of prostate glands affected by hyperplasia (McNeal, 1968; Kohnen and Drach, 1979). The presence of this patchy, but often prominent, mononuclear cell infiltrate is usually not reported routinely by most pathologists unless there is an obvious acute bacterial prostatitis. The aetiology of this lymphoreticular infiltrate is unknown but it has been postulated to be secondary to infective causes (Mardh *et al.*, 1972; Meares and Stamey, 1972), to be a chemical reaction to extravasating prostatic secretions (Odjuno and Elebute, 1971; Attah, 1975) or a combination of both of these (Kohnen and Drach, 1979).

The aim of this study was to characterise the infiltrate, *in situ*, in frozen sections of prostatic tissue using a panel of cell surface specific monoclonal antibodies. To the best of our knowledge, phenotypic characterisation of this “inflammatory”

infiltrate has not been documented previously in the literature. Delineation of the cell subsets within the infiltrate and their tissue distribution within the prostate gland could define more precisely the pathogenesis of this infiltrate.

Patients and Methods

Specimens were obtained, at the time of transurethral prostatic surgery, from 20 patients (mean age 70 years) undergoing elective surgery for suspected prostatic hyperplasia. None had been catheterised pre-operatively. All had normal renal function as assessed by serum urea and creatinine and all had sterile pre-operative urine cultures.

The prostatic chips were snap frozen and sequential frozen sections, 6–8 µm thick, were cut. The sections were allowed to air dry overnight at room temperature and stained within 48 h of tissue resection. Routine haematoxylin and eosin sections were prepared and the histological appearances of

these, and routine paraffin embedded blocks from the same patients, were reviewed by an experienced pathologist (I.D.M.) to confirm the diagnosis of hyperplasia.

Immunohistochemical procedure

The monoclonal antibodies were reacted with tissues using immune complexes of alkaline phosphatase and monoclonal anti-alkaline phosphatase (APAAP complexes) (Cordell *et al.*, 1984). The sections were fixed in acetone for 20 min and then washed in 0.05 M, pH 7.6, Tris-buffered saline (TBS) before applying the monoclonal antibody. The sections were incubated for 1 h in a moist chamber. They were then incubated with rabbit anti-mouse immunoglobulin for 30 min, followed by incubation with APAAP complexes for 30 min. The sections were washed with TBS between incubations. The sections were developed with a veronal acetate buffer solution (VAB) to which Naphthol AS-MX phosphate, levamisole and Fast Red TR were added and counterstained in Mayer's haematoxylin. Negative controls included sections in which the primary antibody was omitted. Positive controls were carried out on human lymph node and tonsil sections to check antibody reactivity and to determine optimal dilutions of antibody.

Monoclonal antibodies

A panel of monoclonal antibodies was used in the study (Table 1).

Examination of specimens and scoring

The sequential sections were examined with a light microscope. Positive cells had red membrane staining and were easily identified. The total number of positive cells in 20 random, consecutive fields was counted (total area = 1.2 mm²). The

relative distribution of positive cells between the epithelial and stromal tissue was also recorded.

From these counts we were able to determine the following:

(i) the distribution pattern of the various cells in the 2 anatomical compartments of the gland, (ii) the percentages of the major cell types within the infiltrate and (iii) the ratio of T-lymphocyte subsets within the 2 anatomical compartments of the gland. The irregular nature of the infiltrate made it impossible to determine accurately the absolute numbers of infiltrating cells.

Berg's stain

Berg's stain is a modified carbol-fuchsin technique, for demonstrating acid-fast material, which stains spermatozoa (Berg, 1953). All of the TURP specimens were stained using this technique. Whole transverse sections from 20 post mortem specimens of prostate (age range 20–80 years) were also stained. Sections of normal testes were used as positive controls.

Statistical analysis

The ratios of the T-lymphocyte subsets within the epithelial and stromal tissues were compared using the Wilcoxon rank sum test.

Results

Morphological characterisation

All of our specimens showed an inflammatory infiltrate, most of which was found in the tissue stroma, with smaller numbers in the epithelial compartment. The histological diagnosis of hyperplasia was confirmed in each case. The infiltrate was graded as light (+) in 10/20 cases, moderate (++) in 7/20 cases and heavy (+++) in the remaining 3 specimens.

Large numbers of cells, reacting with the pan-leukocyte marker CD-45, were seen in all sections examined and in all compartments of the gland. There was no obvious pattern to this infiltration, the distribution of cells being very irregular.

Phenotypic characterisation

T-lymphocytes. The infiltrate was composed mainly of CD-3+ T-lymphocytes which were noted in the epithelial lining of the glands, in the immediate peri-glandular tissue and in the connective tissue stroma (Fig. 1, Table 2).

Using the helper/inducer cell (CD-4) and the cytotoxic/suppressor cell (CD-8) markers, the pat-

Table 1 Monoclonal Antibody Panel

<i>Monoclonal antibody</i>	<i>Specificity</i>
HLLe-1*	Pan-leukocytes
CD-3 (Leu 4)	Pan T-lymphocytes
CD-4 (Leu 3a)	Helper/inducer T-lymphocytes
CD-8 (Leu 2a)	Cytotoxic/suppressor T-lymphocytes
CD-22 (Leu 14)	Pan B-lymphocytes
CD-16 (Leu 7 & 11b)	Natural killer cells
CD-11c (Leu M5)	Monocytes and macrophages
CD-25 (IL-2R)†	Interleukin-2 receptor
HLA-DR+	Activated T-lymphocytes and macrophages

*Scottish Antibody Production unit.

†Dakopatts A/C.

All others obtained from Becton-Dickinson.

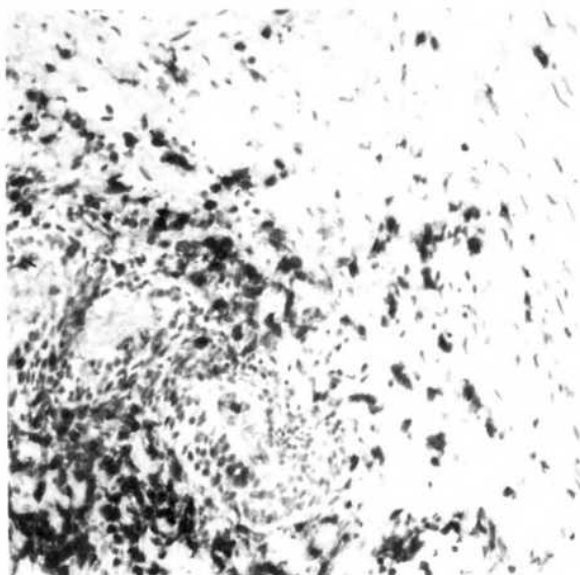


Fig. 1 T-lymphocytes (CD-3+) in the intra-epithelial, periductal and stromal regions. (APAAP technique $\times 124$).

tern of distribution of the subsets was found to vary, with most of the intra-epithelial cells being CD-8+ cytotoxic/suppressor cells (Fig. 2). The difference in the ratio of the 2 subsets in epithelial and stromal tissues is outlined in Table 3 and was statistically significant ($P < 0.01$, Wilcoxon).

B-lymphocytes. Isolated collections of CD-22+ B cells were found in the stroma but these were

Table 2 Percentages of Major Cell Types within the Inflammatory Infiltrate

	T-lymphocytes (CD-3)	B-lymphocytes (CD-22)	Macrophages (CD-11c)
N = 20			
Mean $\pm$ SEM*	63 $\pm$ 2	9 $\pm$ 2	23 $\pm$ 1

*SEM: Standard error of the mean.

Table 3 T-lymphocyte Subset Ratios (CD-4+/CD-8+) within the 2 Anatomical Compartments of the Gland and Overall

	Epithelium (CD-4/CD-8)	Stroma (CD-4/CD-8)	Overall (CD-4/CD-8)
N = 20			
Mean $\pm$ SD*	0.7 $\pm$ 0.4†	1.1 $\pm$ 0.5†	0.9 $\pm$ 0.4

*SD: Standard deviation.

†Statistical analysis: $P < 0.01$ (Wilcoxon Rank Sum Test).

uncommon and solitary B cells were very rarely noted. Plasma cells, as assessed by morphology alone, were also very rarely noted in the sections examined.

Macrophages. The macrophage population constituted $23 \pm 1\%$ of the total infiltrate (Table 2) and was present mainly in the stromal tissue, although small numbers were noted infiltrating among the epithelial cells and in the lumen of some of the glands. The majority of the macrophages reacted with the HLA-DR antibody, as did endothelial cells lining blood vessels and a small number of the T-lymphocytes. Epithelial reactivity with the HLA-DR antibody was not noted.

NK cells

We were unable to demonstrate any CD-16+ natural killer cells in any of the specimens examined.

Berg's stain

We were unable to demonstrate sperm in any of our TURP specimens. This is not surprising, however, since the amount of tissue that is histologically examined is very small in relation to the whole gland. In addition, the age of the patients (mean 70 years) and hospital admission for operation made it unlikely that they had been recently sexually active.

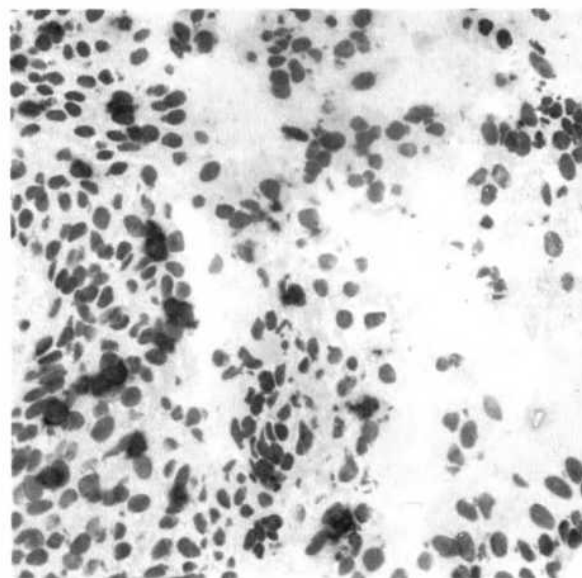


Fig. 2 T-cytotoxic/suppressor cells (CD-8+) among the glandular epithelium. (APAAP technique $\times 284$).

Examination of whole prostate sections from 20 cadavers (age range 20–80 years), however, did reveal intraurethral and intraprostatic spermatozoa in 1 case (age 29 years), although this was not closely related to an inflammatory infiltrate (Fig. 3). This confirms the recently reported finding of spermatozoa in the prostate (Nelson *et al.*, 1988), albeit in a smaller proportion of our cases.

Discussion

It has been postulated that the normal prostate gland is a partially privileged immunological site due to the lack of afferent lymphatics (Gittes and McCullough, 1974) and the immunosuppressive properties of seminal plasma (Ablin *et al.*, 1980; James and Hargreave, 1984). However, spermatozoa are known to be highly immunogenic (Anderson and Tarter, 1982), can penetrate mammalian cells (Bendich *et al.*, 1974) and can alter their antigenic and morphological characteristics (Higgins *et al.*, 1980). We have demonstrated the presence of spermatozoa and the presence of an invariably mild to moderate "inflammatory" infiltrate in prostate glands resected for hyperplasia. We have also shown that this infiltrate is composed mainly of T-lymphocytes, contains a significant number of macrophages, and has small numbers of B-lymphocytes and no natural killer cells.

Phenotypic characterisation showed that CD-8+ cytotoxic/suppressor cells were found predom-

inantly among the epithelium, whilst the CD-4+ helper/inducer cells were more abundant in the stromal tissues. CD-4+ helper T cells predominate in interstitial aggregates in delayed type hypersensitivity reactions (Platt *et al.*, 1983) and the high proportion that we have demonstrated, in conjunction with the prominent resident stromal macrophages expressing HLA-DR antigens, suggest the presence of a cell mediated immune response in the stroma of the prostate. The latter may represent a delayed type hypersensitivity reaction in response to, among other things, the presence of spermatozoa in the prostate.

A prominent CD-8+ cytotoxic/suppressor cell barrier exists in the epithelial compartment of the epididymis (Lord *et al.*, 1977; Ritchie *et al.*, 1984) as a necessary defence against autoimmunisation to sperm antigens. Also, it has been reported to be present in normal prostatic tissue (El-Demiry *et al.*, 1985). This microanatomical arrangement is seen in other organs constantly exposed to antigenic stimuli such as the intestine (Selby *et al.*, 1981; Targan, 1987). Thus it may be seen as a major immunological barrier which prevents antigens from entering the general circulation. This epithelial barrier may be a necessary defence within the prostate gland as intra-prostatic spermatozoa have been described recently in a high proportion of glands (Nelson *et al.*, 1988). We have also demonstrated spermatozoa within the prostate gland, although less commonly than in the latter study.

The presence of spermatozoa in the prostate gland is probably more common than previously realised. Their presence, albeit intermittently throughout adult life, may be an important factor in the aetiology of the "inflammatory" infiltrate so commonly seen. Further studies are needed to establish the frequency of sperm intrusion into the prostate gland.

Acknowledgements

We thank Messrs J. H. Steyn, W. H. H. Garvie and L. E. F. Moffat for providing fresh surgical specimens. We also thank the Grampian Health Board for financial support for this project.

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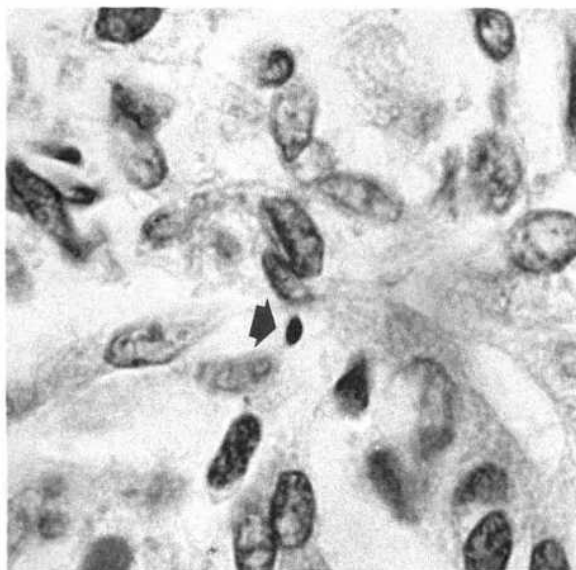


Fig. 3 Berg's stain demonstrating intraprostatic spermatozoa. ($\times 560$).

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The Natural Course of Low Grade, Non-metastatic Prostatic Carcinoma

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Summary—A surveillance study was carried out on 167 patients with low grade, low stage prostatic carcinoma without known metastases; of these, 146 were evaluated, the mean follow-up time being 50 months. Local tumour progression occurred in 77 patients (53%), corresponding to a 5-year cumulative probability of progression of 67%. Ten patients developed metastases, 5 died of prostatic carcinoma and 24 died of other causes. Cox's regression analysis showed that the initial cytological grade of the tumour was of prognostic importance, but initial local tumour stage, prostatic acid phosphatase activity and age had no statistically significant prognostic value. Although the number of patients developing metastases and dying of prostatic carcinoma was low, most tumours seemed to progress locally.

Information on the natural course of untreated prostatic carcinoma is still sparse because the patients in most previous studies had been subjected to anti-tumour treatment. In early studies the reported survival for untreated prostatic carcinoma was poor but in recent years the prognosis has improved (Whitmore, 1984). In the present study the tumour progression rate was investigated in patients with low grade, low stage prostatic carcinoma.

Patients and Methods

Between 1978 and 1982, 167 patients with newly discovered well differentiated (G1) and moderately well differentiated (G2) non-metastatic prostatic carcinoma were included in a surveillance study. In the majority of the patients the tumour was found at routine digital rectal examination and only 11 had symptoms of bladder neck obstruction requiring transurethral resection of the prostate within 12 months of diagnosis. Eighteen patients were below 60 years of age at the beginning of the study, 62 were between 60 and 70 years and 66 were above

70 years of age. In all cases the diagnosis and the grade of the tumours were assessed cytologically on samples obtained by transrectal fine needle aspiration (FNA) biopsies. These biopsies were evaluated according to the criteria described by Esposti (1971). Local tumour stage was assessed by digital rectal examination and the findings were recorded in a standard drawing and a statement in the case records. The local tumour stage was defined according to the criteria of UICC (1978). The status of metastatic lesions was evaluated by radio-isotope scanning of the skeleton and analysis of prostatic acid phosphatase (PAP) by a tartrate inhibited enzymatic assay. The patients were followed up regularly at intervals of 3 to 6 months. The clinical status, local tumour stage and PAP were recorded at each visit and a bone scan was carried out at 12 and 18 months. Local progression was defined as an increase of 25% or more in the largest diameter of the tumour infiltrate as judged from the serial drawings and case records. Surveillance was interrupted if rapid local progression and/or development of metastases occurred and anti-tumour treatment was initiated.

An analysis was made of 146 patients; 10 patients had incomplete records and 11 were lost to follow-

up. The median age of the 146 patients at diagnosis was 68 years (range 38–89); 104 had G1 and 42 had G2 tumours; 13 had T1, 98 had T2 and 35 had T3 tumours. Cox's proportional hazards regression model (Cox, 1972) was used for statistical analysis. Rate ratios were estimated as e^{β} and 95% confidence intervals as $e^{\beta \pm 1.96 \times \text{S.E.}}$, where β is the regression coefficient of the Cox model and S.E. the standard error of the regression coefficient. Local progression and/or development of metastases while the patients were still untreated were used as endpoints in the analysis. Patients without local progression at the time of death (17), during follow-up (52) or at the start of anti-tumour treatment (3) were treated as censored observations.

Results

The median observation time of patients while still untreated was 50 months (range 7–135). During this time, local tumour progression occurred in 77 patients, which corresponds to a cumulative 5-year probability of progression of 67%, and 10 patients developed metastases, corresponding to a 5-year probability of 7% (Fig. 1). Twenty-nine patients died during follow-up, 5 (3%) from prostatic carcinoma and 24 (16%) from other causes. The initial tumour grade and stage of the 5 patients who died from prostatic carcinoma are summarised in Table 1.

G1 tumours progressed at a significantly slower rate than G2 tumours ($P=0.009$) (Fig. 2). Patients with a high local tumour stage tended to progress faster than patients with a low local tumour stage (Fig. 3), but these differences were not statistically

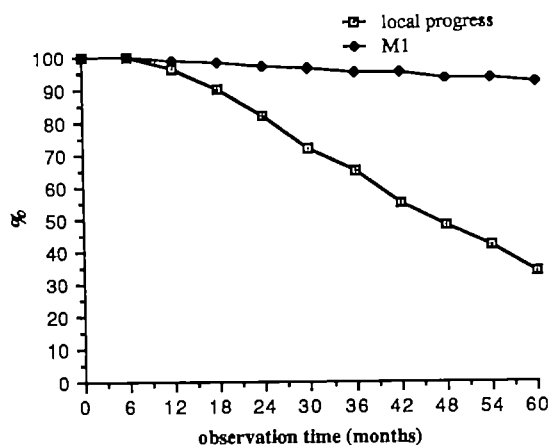


Fig. 1 Relative number of patients with no evidence of metastases and no local progression during the observation time.

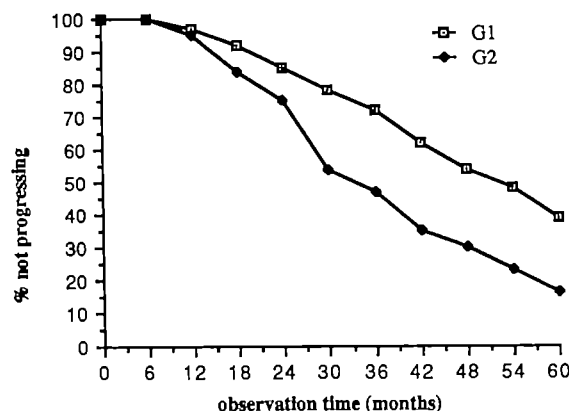


Fig. 2 Relative number of patients with well (G1) and moderately well (G2) differentiated prostatic carcinoma not progressing locally during the observation time.

significant when analysed for trend ($P=0.10$). The initial value of PAP was not of prognostic value, nor was the age of the patient at presentation ($P=0.17$ and $P=0.93$ respectively). Further analysis with the multivariate Cox regression method, adjusting for the correlation between variables, still showed that initial cytological grade had a significant prognostic value (Table 2).

Discussion

The natural course of prostatic carcinoma is not fully known. In earlier studies, patients with untreated prostatic carcinoma had a poor survival rate. In a review of 200 patients diagnosed between 1934 and 1943 and treated with transurethral resection alone, 40% survived for 5 years and only 18% were alive after 10 years (Hanash *et al.*, 1972).

More recently, improved survival and relatively long observation times without tumour progression have been reported. In 45 untreated patients with stage B prostatic carcinoma, 15 (33%) showed

Table 1 Initial Age, Cytological Grade and Local Tumour Stage of Patients who died of Prostatic Carcinoma

Patient no.	Age (years)	Cytological grade	Local tumour stage
1	73	G1	T2
2	79	G2	T3
3	78	G1	T3
4	61	G1	T2
5	63	G1	T3

G1 = well differentiated, G2 = moderately well differentiated.

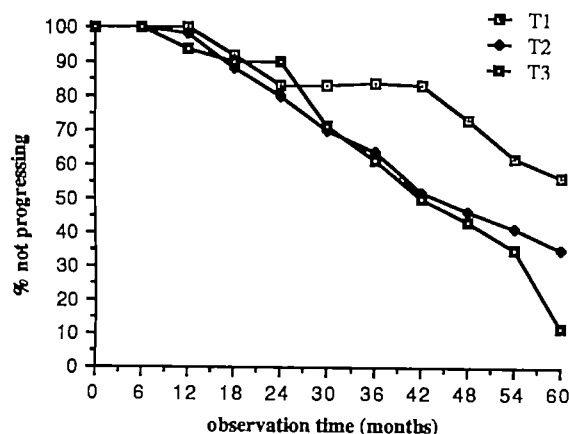


Fig. 3 Relative number of patients with T1, T2 and T3 prostatic carcinoma not progressing locally during the observation time.

tumour progression after a mean observation time of 59 months, while in the remaining 30 patients (67%) there was no clinical evidence of progression after a mean observation time of 79 months (Whitmore, 1984). A progression rate of 9% was reported in a group of untreated patients with VACURG stage I and II tumours after observation for 12 to 36 months (Lingårdh *et al.*, 1983). In another group of patients with VACURG stage II tumours, the 5-year survival rate was 80%, which was comparable to the expected survival (Byar *et al.*, 1981). Parker *et al.* (1985) reported a 70% five-

year survival rate in patients with non-metastatic prostatic carcinoma with no anti-tumour therapy.

These findings of relatively non-aggressive behaviour in prostatic carcinomas in defined groups of patients are consistent with the findings in the present study where, although the local progression rate was 53%, only 7% of the patients developed metastases after a mean observation time of 50 months. Three patients were observed for more than 100 months without showing any progression of tumour. The histological grade of prostatic carcinoma has been correlated to prognosis (Grayhack and Assimos, 1983; Parker *et al.*, 1985; Fordham *et al.*, 1986). A similar correlation was found when the grade was defined on cytological specimens (Esposti, 1971). The correlation between higher grade and a worsening prognosis was not, however, confirmed by other investigators (Epstein *et al.*, 1986; Stephenson *et al.*, 1987; Adolfsson and Fåhræus, 1988). In the present series, cytological grade was of statistically significant prognostic value with regard to locally progressive disease. The number of patients developing metastases in the present series was too small to permit statistical evaluation.

Whitmore (1984) suggested that local tumour stage was of prognostic value. In the present series we could find only a trend towards faster progression locally with increasing local tumour stage and the differences were not statistically significant. Our

Table 2 Multivariate Cox's Regression Analyses of Relation of Local Progression to Cytological Grade, Local Tumour Stage, Prostatic Acid Phosphatase (PAP) and Age at Diagnosis in Patients with Untreated Prostatic Carcinoma.

Variable category	No. of patients	Rate ratio*	95% confidence interval	Statistical significance
Grade				
Well differentiated	104	1.00	—	
Moderately well differentiated	42	2.05	1.2–3.5	$P=0.01$
Tumour stage				
T1	13	1.00	—	
T2	98	1.56	0.7–3.7	
T3	35	1.93	0.7–5.1	$P=0.19†$
PAP				
Normal	122	1.00	—	
Elevated	24	1.66	0.9–3.1	$P=0.12$
Age (years)				
< 70	80	1.00	—	
≥ 70	66	0.81	0.5–1.3	$P=0.39$

* Ratio of the rate of patients progressing in each category to that in the reference category (the first category for each variable). Adjusted for other variables listed.

† Test for trend.

findings agree with those of Parker *et al.* (1985), where there was no difference in survival between patients with T1, T2 and T3 tumours; the prognosis was better in those with T0 tumours and worse in those with T4 tumours. The results in the present series, however, are probably biased since most patients were T2 and very few were T1 and T3. Our patients were highly selected initially, including only well and moderately well differentiated carcinomas, and the majority of patients had T2 tumours. No poorly differentiated or T4 tumours were included. All patients were regarded as M0 initially. This bias towards low grade, low stage tumours explains the small number of patients who developed metastases, but given enough time most tumours seemed to progress locally. Our findings are comparable with those of George (1988), where 84% of patients with prostatic carcinoma without treatment progressed locally and 10% developed metastases during a 5-year follow-up. Similar figures are reported by Johansson *et al.* (1989) in another series of patients during surveillance. The rates of patients developing metastatic disease in the present series and in that of George (1988) are comparable to the rates reported in patients with G1-2, T1-2 prostatic carcinoma after external irradiation (Hanks *et al.*, 1988; Zagars *et al.*, 1988) and radical prostatectomy (Ritchie *et al.*, 1988). The rate of local recurrence in these studies was low. External irradiation and radical prostatectomy do not seem to be of benefit regarding the development of distant metastases, though they probably result in local control of the tumour.

The small number of patients who developed metastases and died of prostatic carcinoma in the present series supports the concept that deferred treatment may be recommended in low grade, low stage prostatic carcinoma, particularly if the life expectancy of the patient is short. Since the median observation time was only 50 months, it is not possible to draw any conclusions regarding deferred treatment in patients with a long life expectancy.

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Midnight Removal: an Improved Approach to Removal of Catheters

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Summary—There is no recognised policy regarding the timing of urethral catheter removal, although early morning removal is commonly practised. Removing the catheter at midnight allows patients to return to a normal voiding pattern more rapidly and to leave hospital earlier.

When a urethral catheter is removed, early discharge of the patient depends on a rapid return to a normal voiding pattern. Delay often occurs because of an initial period of urinary frequency and low volume micturition.

There does not appear to be a general policy on the timing of urethral catheter removal, although early morning removal, around 6 am, seems to be fairly common practice. The rationale behind this policy is the avoidance of acute urinary retention, in the early hours of the following morning, in those patients who cannot void normally after removal of their catheters. We have identified a number of problems associated with this policy. They may be summarised under the following headings.

Urological problems

Patients who have voiding problems are often not identified until late in the evening of the day of catheter removal. Management decisions are therefore often taken by "duty staff" who may not be directly involved in the care of the patient. Lack of communication occasionally leads to incorrect decisions and definitive treatment may well be delayed until the following morning business round.

Nursing problems

The first few hours of the morning shift are often the busiest time of the day for ward nursing staff.

The "Nursing Process" record has to be completed, patients are lifted from their beds, breakfast is distributed, "Report" is given, the early morning drug round occurs, the nursing personnel change and the doctors arrive for their early rounds. The removal of a urethral catheter therefore falls low on the priority of nursing duties and consequently, on the busy and often understaffed wards on which most of us work, the removal is often delayed. Occasionally patients have required recatheterisation in the early hours of the morning because of such delays.

Patient problems

Patients who have been catheterised for a variety of urological procedures often have long-standing histories of voiding difficulties. The period following catheter removal is often, therefore, an extremely anxious period for the patient. We have observed that there is often a period of urinary frequency with small voided volumes following catheter removal and these initial abnormalities in the voiding pattern cause the patient considerable distress.

In view of these adverse factors we conducted a prospective trial to study the effects of catheter removal at midnight.

Patients and Methods

All patients requiring urethral catheterisation who were admitted to this unit (n=108; 84 males, 24 females) were entered alternately into 1 of 2 groups:

Read at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

catheters were removed at midnight in Group A and at 6 am in Group B. Twenty-two patients were excluded from the trial, usually due to pre-existing urinary tract infection confirmed on a mid-stream urine sample; thus 86 patients remained in the study (Table 1).

The following variables were recorded:

- (1) The actual time of catheter removal (the object of this part of the study was to assess the problems encountered by the nursing staff in removing catheters at a particular time of day). Catheters removed later than 30 min after the prescribed time were adjudged to have been removed "late" and were recorded to the nearest hour on a standard fluid balance chart.
- (2) The volume of the first void (ml).
- (3) The time to the first void (h).
- (4) The interval between catheter removal and discharge from hospital.

In addition to these factors, the operative procedure undertaken, the presence or absence of post-operative urinary tract infection and the administration of night sedation were noted for each patient.

Table 1 Details of Patients

Reasons for catheterisation	Group A (n=40)	Group B (n=46)
Transurethral resection of prostate	10	13
Urethrotomy/dilatation	6	12
Bladder neck incision	10	6
Transurethral resection of bladder tumour	4	6
Percutaneous colposuspension	3	3
Post-operative (surgical)	5	3
Miscellaneous	2	3

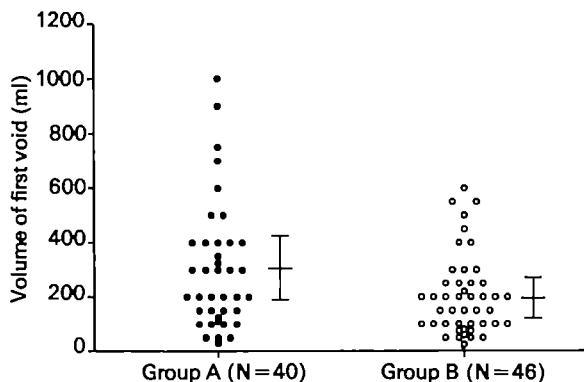


Fig. 1 Comparison of the volume of first void in Groups A and B (mean $\pm$ 1/2 SD).

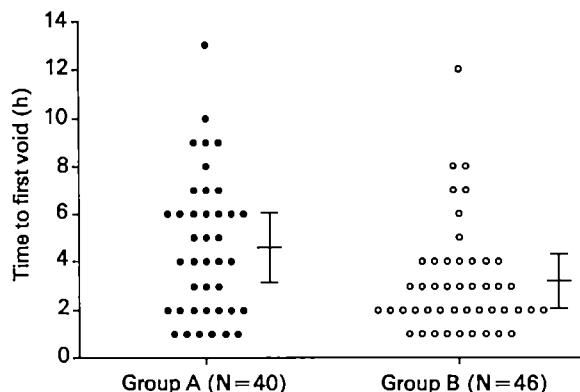


Fig. 2 Comparison of the time to void in Groups A and B (mean $\pm$ 1/2 SD).

Results

The results showed that there was a significant difference between the volume of the first void (Fig. 1) and the time to the first void (Fig. 2) when comparing the 2 groups.

Patients whose catheters were removed at midnight (Group A) passed far greater volumes at first void than did patients whose catheters were removed at 6 am (Group B). The time to first void was far greater in Group A patients than in Group B. More than half of the patients in Group A (58%) were discharged home later that same day, compared with fewer than a quarter in Group B (22%). Only 5% of the catheters in Group A were removed later than instructed; in Group B this figure was as high as 30% (Fig. 3). The results are summarised in Table 2.

Discussion

The results confirm several advantages of catheter removal at midnight compared with early in the morning. The time to the first void was significantly increased and consequently the volume of the first void was greater. We observed that, following their

Table 2 Results

	Group A (n=40)	Group B (n=46)	P
Volume of first void (ml)	307	197	<0.05
Time to first void (h)	4.6	3.2	<0.02
Discharge same day (%)	23 (58)	10 (22)	<0.001
Catheter removal on time (n%)	38 (95)	32 (70)	<0.02

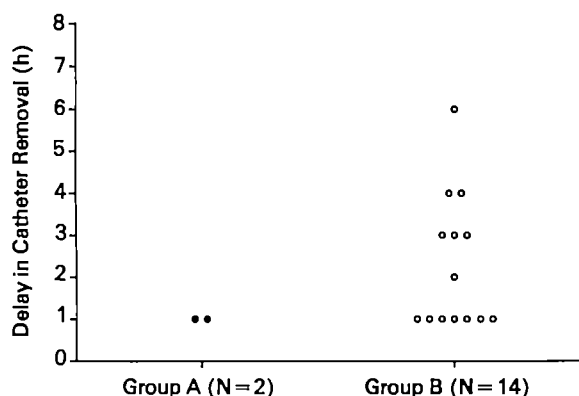


Fig. 3 Comparison of late removal of catheter in Group A (n = 2, 5%) and Group B (n = 14, 30%).

first void, the patients whose catheters were removed at midnight returned to a more regular, normal voiding pattern faster and this allowed earlier discharge from hospital. The mechanisms behind these observations are unclear but are probably related to the fact that many of the patients in Group A slept through the period immediately following catheter removal; 82.5% of all patients received night sedation on the evening of their catheter removal, allowing a rapid return

to sleep of those whose catheters were removed at midnight, but apparently removing little of the anxiety and distress observed in patients waiting for catheter removal at 6 am. Some of the patients in Group A slept through catheter removal!

We also found that 30% of catheters due for removal at 6 am were removed later than the appointed time, confirming the impression that early morning is an inconvenient time for the nursing staff.

It was concluded that a policy of catheter removal at midnight confers advantages to both urological and nursing management. It is more agreeable to the patient and allows a quicker return to a normal voiding pattern. Earlier discharge from hospital is thus possible in the majority of cases.

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Risk of Recurrent Stricture following Internal Urethrotomy

Prospective Ultrasound Study of Distal Male Urethra

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Summary—A group of 60 patients was examined prior to surgery in a prospective ultrasound study of the distal male urethra to predict the individual rate of stricture recurrence after internal urethrotomy. The patients were divided into 2 groups according to the ultrasound findings. One group had no evidence of scarred tissue and no recurrence was predicted. The other group did have periurethral scarring and stricture recurrence within approximately 6 months was predicted. We present the ultrasound findings and discuss the accuracy of the predictions. Correct prognoses were made in 92.9% of cases.

A new method of ultrasound investigation of the distal male urethra has been developed which demonstrates both intra- and extra-urethral strictures and scarring (Gluck *et al.*, 1988; McAninch *et al.*, 1988; Merkle and Wagner, 1988).

In a retrospective study, Merkle and Wagner (1988) showed that strictures recurred at the primary site only when significant periurethral scarring was revealed on the pre-operative ultrasound scan. It remained unclear whether it was possible to predict which patients would have stricture recurrence at the primary location after internal urethrotomy.

A prospective study was therefore carried out on more than 50 patients in order to establish the reliability of such predictions.

Patients and Methods

Sixty patients were investigated pre-operatively by ultrasound after X-ray confirmation of strictures in the bulbous or distal urethra. With 1 exception, all patients underwent an internal urethrotomy as described by Sachse (1974). Deep incisions were made at the 12, 4 and 8 o'clock positions followed

by instillation of cortisone jelly into the urethra and a 20F catheter was left *in situ* 24 h. Prior to the procedure, urinary infections were treated by antibiotics.

Patients were divided into 2 groups according to the sonographic findings. Group A comprised patients with periurethral scars and Group B included patients without periurethral scarring (Fig. 1). It was predicted that Group A patients would have a recurrent stricture at the primary location and Group B patients would not.

The ultrasound technique has been described by McAninch *et al.* (1988) and Merkle and Wagner (1988). The urethra is filled with saline solution and a 7 MHz scanner is used to outline both urethral and periurethral structures. Strictures are shown as an indentation or narrowing of the lumen and scars are visible as peristricatural "white strings" (Fig. 2).

Follow-up X-ray and ultrasound examinations were made at least 6 months after surgery.

Results

Of the 60 patients who entered the study, 56 were evaluated statistically after 6 months. One patient had suffered from cerebrovascular bleeding and had an indwelling catheter because of incontinence,

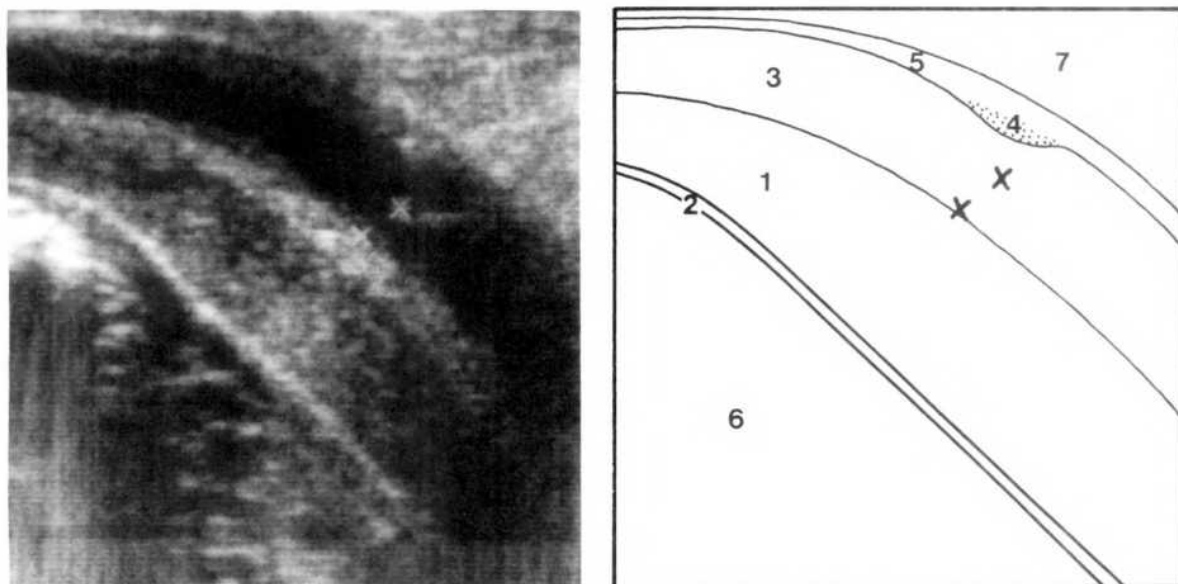


Fig. 1 Stricture in bulbous urethra without periurethral scarring (between x and x). 1: Corpus cavernosum. 2: Buck's fascia. 3: Urethral lumen (saline solution). 4: indentation of urethral stricture. 5: Corpus spongiosum. 6: Abdomen. 7: Contact jelly.

1 patient had undergone the first stage of open urethroplasty, 1 had died of myocardial infarction and 1 refused follow-up investigations. The results are shown in the Table. Local stricture recurrence was predicted correctly in 92.9% of cases.

In 4 of the 56 cases the prediction was not as expected. In 3 patients no recurrence was seen after

6 months but 2 of them did develop late recurrences after 14 and 16 months respectively. Thus the correct prognosis in group A was 18/19 patients (94.8%).

Only 1 patient in group B had a recurrent stricture. For unknown reasons he had undergone a series of urethral dilatations prior to follow-up

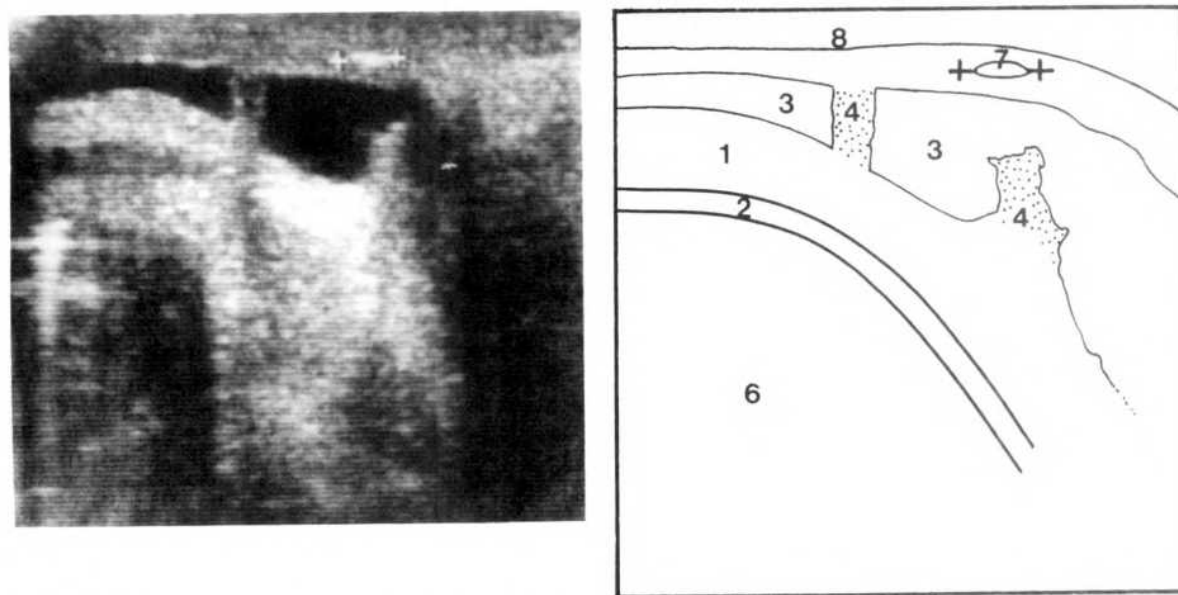


Fig. 2 Stricture in bulbous urethra with periurethral scarring (between + and +). 1: Corpus cavernosum. 2: Buck's fascia. 3: Urethral lumen (saline solution). 4: Indentation of urethral stricture. 5: Corpus spongiosum. 6: Abdomen. 7: Peristriktural scar (fibrotic tissue). 8: Contact jelly.

Table Prognosis of Recurrent Strictures (after more than 6 months)

<i>Correct prognosis: 52/56 (92.9%)</i>	
Correct prognosis of recurrence: 16/19* (84.2%)	Correct prognosis of non-recurrence: 36/37 (97.3%)
Incorrect prognosis of recurrence: 3/19* (15.8%)*	Incorrect prognosis of non-recurrence: 1/37 (2.7%)

* 2 late recurrences after 14 and 16 months. (Final rate of correct prognosis: 94.8%; wrong prognosis: 5.2%).

despite a satisfactory urinary flow rate. This iatrogenic trauma of the urethra might have caused the new stricture.

The strictures were mostly caused by catheterisation for non-urolological reasons during intensive care (37 cases). Further reasons for stricture formation were: transurethral resection of the prostate or bladder tumours (10 cases), sexual intraurethral stimulation by a wire, gonorrhoea, Fournier's gangrene (1 case each), catheterisation during open surgery of the bladder (3 cases). In 3 further cases no reasons for stricture formation was found.

It is noteworthy that all but 1 of the patients in group A were amongst those who had been catheterised for more than 3 days.

Discussion

In a retrospective study by Merkle and Wagner (1988) a correlation was found between periurethral scarring seen on pre-operative ultrasound scans and the subsequent recurrence of stricture following internal urethrotomy. The results of the present study have confirmed these findings and also shown that the long-term successful outcome of internal urethrotomy can be predicted by the absence of

periurethral scarring. It is therefore no longer necessary to discuss statistical recurrence rates with a patient before advising surgery to correct his urethral stricture (Hjortrup *et al.*, 1983; Smith *et al.*, 1983; Netto *et al.*, 1989). Patients without periurethral scars can be told there is little risk of stricture recurrence following internal urethrotomy and those with scars can be offered alternative procedures.

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Long-term Results of Carbon Dioxide Laser Treatment of Meatal Condylomata Acuminata

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Summary—A group of 74 men who underwent carbon dioxide laser treatment of meatal condylomata were observed for an average of 18 months. The cure rate after 1 treatment of isolated meatal lesions was 78%; the presence of external lesions lowered the rate to 32% and additional external and urethral warts to 25%. Following multiple treatments all but 6 patients were cured; 83% of the recurrences developed within 3 months. One urethral and 6 meatal strictures occurred more than 3 months after treatment; 9 patients had a spraying stream many years after treatment and 2 complained of frequency.

Several methods are available for the treatment of genital condylomata. Topical podophyllin is still the first choice for eradication of external genital warts but the ulceration and strictures which it may cause and its inconvenience make it less attractive for the treatment of meatal and urethral condylomata.

Photocoagulation by CO₂ lasers has become increasingly popular over the last decade (Fuselier *et al.*, 1980; Rosenberg *et al.*, 1982). However, the study groups are small, the patients unselected and the length of follow-up too short for satisfactory evaluation of the results.

The aim of this study was to assess the long-term results of CO₂ laser treatment of meatal condylomata in males.

Patients and Methods

A series of 88 males underwent CO₂ laser treatment for meatal condylomata in this department between 1984 and 1988. All but 16 had previously been treated with podophyllin, interferon, cryosurgery or excision. They were followed up and, if necessary, re-treated until cured. By February 1989, 74 patients (median age 24 years, range 19–37) had been followed up for more than 1 month. A questionnaire

was sent to these patients in order to evaluate recurrences and voiding complications and the patients were divided into 3 groups. In Group A were 32 patients with solitary meatal warts; Group B included 34 patients with meatal and external warts and Group C comprised 8 patients with meatal, urethral and external warts.

Coexisting disorders

Twelve patients had a history of gonorrhoea and 7 had chlamydial urethritis. At referral, cultures showed growth of *Neisseria gonorrhoea* in 1 and *Chlamydia* in 3 patients. Four patients had haematuria, 1 complained of dysuria and 7 of a spraying urinary stream. Five patients, previously treated with podophyllin, had meatal stenosis at referral.

Operative technique

Photocoagulation of meatal and external condylomata was carried out under general anaesthesia with a Sharplan 733 CO₂ laser using a hand-held focusing device with an effect between 4 and 10 W and a focused spot diameter size of approximately 2 mm. Some patients had additional treatment with podophyllin or electrocautery.

Urethroscopy was always performed and urethral condylomata were cauterised with a needle electrode. Meatotomy, if required, was done by incising

the meatus at 12 o'clock. When the treatment was extensive an indwelling catheter was left in place overnight. All patients were advised to use condoms until cured.

Results

The results of treatment are shown in Table 1 and the time to meatal recurrences after 1 laser treatment in Table 2.

One diabetic developed a superficial infection in the necrotic area. Urethral condylomata developed in 1 patient in Group A and 4 in Group B. Stricture of the urethra occurred in 1 patient and stenosis of the meatus in 6, necessitating urethrotomy, meotomy or dilatation. Nine patients complained of a spraying urinary stream years after laser treatment and 2 of frequency.

Discussion

Our cure rates of 25 to 78% were much lower than those in previous reports of treatment of genital condylomata with the CO₂ laser (Rosemberg *et al.*, 1982; Ferenczy, 1984; Scott and Castro, 1984) but this is probably due to longer observation periods and/or different localisation.

Long-term cure rates after laser treatment were disappointing in a randomised study by Duus *et al.* (1986), who compared electrocauterisation and CO₂ laser treatment of mostly external lesions. In addition, no difference was found between the 2 forms of treatment.

Many methods are available for the treatment of condylomata and new methods are often introduced before proper appraisal of the preceding ones. In the only controlled study of urethral condylomata,

the cure rates were 33 and 53% for 5-fluorouracil and podophyllin respectively (Wallin, 1977). Problems arise in carrying out a satisfactory investigation because recurrences may be grossly invisible; using an operating microscope, however, a recurrence rate of 66% for external lesions was found after 4 months (Carpiniello *et al.*, 1987), which resembles our figures.

The failure of laser treatment may be attributed to inadequate power applications, although many of our patients had recurrences or residual lesions after the first treatment. Increasing the power may increase the number of complications. The amount of transmitted energy (power density) varies with a factor of 100 for varying spot sizes, focus distances and type of laser. Another possible cause of failure is reinfection from an untreated sexual partner, although our patients were advised to use condoms.

We always performed urethroscopy in patients with meatal warts in order to detect hidden lesions in the proximal urethra, but these occurred in only 11% of cases. Since 5 patients developed proximal lesions after urethroscopy, we have changed our policy and now examine recurrences only. On the other hand, undetected lesions in the urethra may be hazardous to the female sexual partner, as human papilloma virus is claimed to be carcino-

Table 2 Time to 30 Meatal Recurrences after 1 Laser Treatment

Months	No. of patients
0-3	25
3-6	2
6-9	1
24-29	2

Table 1 Long-term Results of Laser Treatment of Condylomata in 74 Patients

	Group A Meatal (n=32)	Group B Meatal and external (n=34)	Group C Meatal, urethral and external (n=8)
Median observation time and range (months)	20 (1-54)	14 (1-56)	34 (2-49)
Cure rate after 1 treatment (95% confidence limits)	78% (60-91)	32% (17-51)	25% (3-65)
Percentage of patients with			
Additional podophyllin or electrocauterisation	9	18	37
2 laser treatments	6	26	25
3-6 laser treatments	6	24	13

genic to the female cervix. Other methods, such as the demonstration of DNA sequences of human papilloma virus in the urine (Carpiniello *et al.*, 1987), may be an alternative in the future.

Unlike other investigators (Rosemberg *et al.*, 1982; Ferenczy, 1984), we found that several patients complained of a spraying urinary stream many years after treatment. Podophyllin did not cause similar problems.

In conclusion, the success of laser treatment of meatal condylomata has been exaggerated. Patients with additional external lesions often require several procedures before cure is achieved, although isolated meatal lesions are often cured by 1 treatment. In view of the fact that only a minority of patients have proximal urethral lesions, urethros-copy can be limited to those with recurrences.

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Validation of a Non-invasive Device to Measure Intracavernous Pressure as an Index of Penile Rigidity

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Summary—Many authors agree with the importance of developing devices to measure penile rigidity. The devices that have been developed over recent years have defined penile rigidity in terms of stiffness. Penile stiffness, however, is believed to result from an increase in intracavernous pressure. The device presented here was therefore designed to estimate intracavernous pressure, rather than penile stiffness, as an index of penile rigidity. Validation of the penile cuff device was achieved by simultaneously recording penile cuff pressure and intracavernous pressure on patients undergoing artificial erections. The results showed a linear relationship and highly positive correlation coefficients between the 2 measures. The results demonstrate that the penile cuff may be used to estimate intracavernous pressure as an index of penile rigidity. The findings are discussed in terms of the possible applications of the cuff as a clinical tool to measure both penile tumescence and penile rigidity.

The assessment of nocturnal penile tumescence (NPT) as developed by Fisher *et al.* (1975, 1979) and Karacan *et al.* (1970, 1972, 1975, 1978a) has, until recently, been the most widely used technique to establish a differential diagnosis between organic and psychogenic erectile dysfunction. Patients presenting with erectile dysfunction and showing abnormal NPT recordings usually receive a diagnosis of organic erectile dysfunction, while patients presenting with erectile dysfunction and showing NPT recordings in the normal range receive a diagnosis of psychogenic erectile dysfunction. NPT recordings, however, are not devoid of methodological flaws. Patients can show NPT recordings in the normal range while still having insufficient penile rigidity to allow vaginal penetration (Wein *et al.*, 1981; Kaneko and Bradley, 1986). Based on the above criteria, these patients would receive a diagnosis of psychogenic erectile dysfunction when the rigidity problem, which went unnoticed, could be of organic origin. For this and other reasons, such as individual variability and poor therapeutic

index (Morales *et al.*, 1982; Bradley *et al.*, 1985; Bertini and Boileau, 1986; Condra *et al.*, 1986), several authors have argued that standard NPT recordings are not sufficient to establish diagnoses of sexual dysfunction.

Standard NPT recordings are assessed with a penile strain gauge which consists of a thin rubber tube filled with mercury. As erection occurs, distension of the penis stretches the rubber tube, which thins the mercury column and increases its resistance (Rosen and Keefe, 1978). The penile strain gauge therefore measures tumescence in terms of changes in penile circumference, but it has been argued that it cannot measure penile rigidity (Bradley *et al.*, 1985). Penile rigidity is defined in terms of penile stiffness and results from an increase in intracavernous pressure (ICP) (Lavoisier *et al.*, 1986, 1988a,b; Frohrib *et al.*, 1987). As the strain gauge has inherent elastic properties, it cannot measure penile stiffness or be sensitive to changes in pressure such as changes in ICP. Several studies have demonstrated that penile tumescence was poorly correlated with intracavernous pressure, especially at full tumescence (Metz and Wagner,

1981; Michal *et al.*, 1983; Wespes and Schulman, 1984).

The need to obtain a measurement of penile rigidity in addition to penile circumference has led to the development of various techniques and devices. Techniques such as the stamp ring (Barry *et al.*, 1980; Marshall *et al.*, 1982; Bertini and Boileau, 1986) and devices such as the snap gauge (Ek *et al.*, 1983) improved the earlier inferential techniques based on NPT recordings (Kenepp and Gonick, 1979) or the waking method using the buckling force (Bradley, 1987; Karacan *et al.*, 1978b). These techniques, however, do not allow continuous measurement of rigidity, so that the frequency and duration of nocturnal erections cannot be recorded.

Among new devices, Virag *et al.* (1985) developed a rigidmetre made of an open metal ring and closed with an elastic strip. The elastic component of the device, however, prevents precise measurement of penile rigidity since part of the penis's stiffness is lost during the expansion of the elastic material. Devices such as the Rigiscan (Bradley *et al.*, 1985), in contrast, provide sophisticated measurement of penile rigidity. The device consists of a loop which self-adjusts around the penis. At discrete but regular intervals a force of 340 g (12 oz) is applied on to the loop and the resulting loop displacement is translated into a measure of penile rigidity. The Rigiscan device therefore defines rigidity in terms of stiffness and measures the axial rigidity of the penis as the circumferential force exhibited by the penis against an external load (Bradley *et al.*, 1985). Further studies on the Rigiscan showed that it correlated with intracavernous pressure (Frohib *et al.*, 1987), which is generally recognised as the physiological event responsible for penile rigidity (Lavoisier *et al.*, 1986, 1988a,b; Frohib, 1987).

We describe a new device which estimates penile rigidity directly in terms of intracavernous pressure. Rather than defining penile rigidity in terms of penile stiffness, the device estimates the physiological event responsible for stiffness. It also allows a non-invasive assessment of intracavernous pressure which is in contrast with the direct but invasive assessment of ICP using implanted needles.

Patients and Methods

Nine patients with erectile dysfunction participated voluntarily in the study. They ranged in age from 30 to 55 years (average 43.8).

Penile rigidity was assessed with a pressure cuff (Medasonic) normally used for ultrasonography.

The cuff is made of a non-elastic tissue band, 12 × 2.5 cm, and is covered on its inner lining with a flexible plastic container filled with water. It was connected to a pressure transducer (Hewlett Packard Model 12805N) which recorded changes in water pressure. The transducer signal was amplified with a pressure amplifier and transmitted to a Tecmar data acquisition (Lab Master) board installed into an IBM-PC/XT personal computer. The sampling frequency was 20 Hz, which gave a time resolution of 50 ms.

In order to obtain a reliable measure of intracavernous pressure, devices should be made of non-elastic material. The non-elastic property of the penile cuff was therefore assessed prior to the experimental phase. The cuff was wrapped around a test bladder which was connected to a pressure gauge. A penile strain gauge was placed around the cuff and the pressure inside the test bladder was increased from 0 to 1300 mmHg over 50 trials. No change in the circumference of the cuff was observed during these trials, thereby demonstrating its non-elastic property.

The experimental phase then proceeded and consisted of simultaneously recording changes in ICP and in penile cuff pressure (PCP) during artificially induced erections. The procedure for artificial erection consisted of disinfecting and anaesthetising the penile area and inserting a butterfly needle No. 19 into the left corpus cavernosum. The needle was connected to a Travenol pump which perfused physiological saline at a controlled flow. Intracavernous pressure was recorded from a butterfly needle No. 21 inserted into the right corpus cavernosum. The needle was connected to a pressure transducer and the resulting signal was amplified and connected to the computer data acquisition board (channel 1).

The penile cuff pressure was assessed by tightly wrapping the cuff around the penis, placing the plastic container against the penis. The cuff was closed with a velcro strap and 2 ml of water injected into the plastic container to obtain a baseline pressure of 50 mmHg. The cuff was also connected to the pressure transducer, amplifier and connected to the computer data acquisition board (channel 2). The sampling frequency was again set to 20 Hz.

Results

Figure 1 shows the relationship between penile tumescence and intracavernous pressure. As can be seen, the recording from the penile strain gauge increased rapidly during the early phase of erection

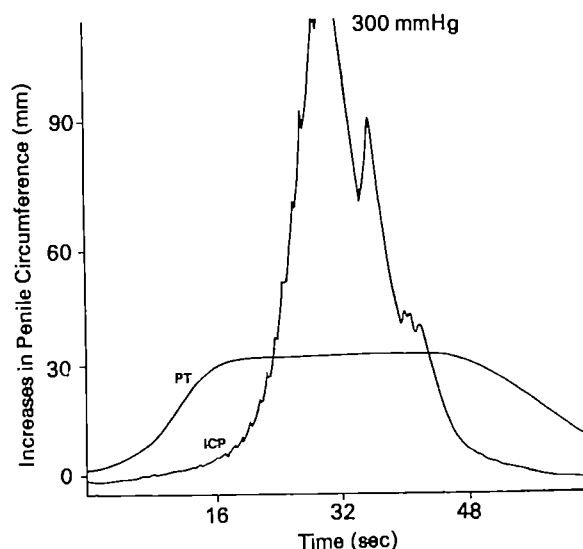


Fig. 1 Polygraph tracing illustrating the relationship between changes in penile tumescence (PT) and changes in intracavernous pressure (ICP).

but levelled off at full tumescence. ICP recording, in contrast, increased slowly during the early phase of erection and increased drastically once full tumescence was reached. This graphical representation illustrates the poor relationship between changes in penile tumescence, as measured by the strain gauge, and changes in ICP, especially at full tumescence.

Figure 2 illustrates the relationship between changes in penile cuff pressure and changes in

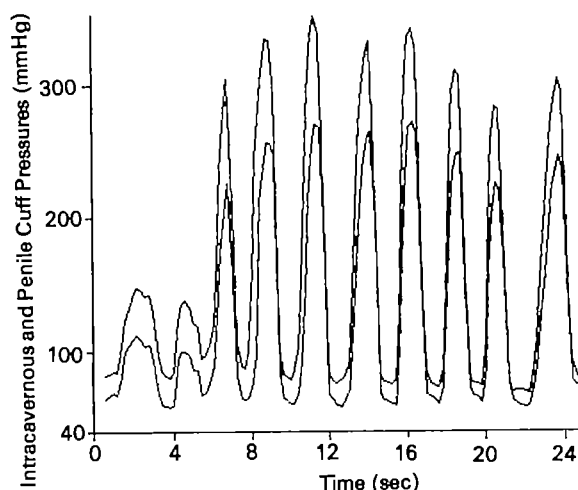


Fig. 2 Polygraph tracing illustrating the relationship between changes in intracavernous pressure (lower line) and changes in penile cuff pressure (upper line).

intracavernous pressure. The 2 recordings varied simultaneously and in the same direction, which suggests that they both recorded the same physiological event. This strong relationship between PCP and ICP was substantiated by the correlation coefficients, which are summarised in Table 1. Individual coefficients varied from 0.85 ($P < 0.001$) to 0.99 ($P < 0.001$) and the overall correlation coefficient between PCP and ICP was 0.96 ($P < 0.001$).

Figure 3 illustrates the scatter diagram and regression line for the subjects' data and Table 2 summarises the components of regression analysis. The regression line demonstrates a linear relationship between penile cuff pressure and intracavernous pressure and the resulting equation Y (estimated ICP) = $6.25 + 0.84 X$ (observed PCP) shows how intracavernous pressure can be estimated from the penile cuff. The percentage of explained variance shows that the measure taken from the cuff accounts for 93% of the variation in intracavernous pressure. The slope of the regression line (0.84) is close to the 45° line (slope of 1.00) which indicates that the variation in the penile cuff pressure is almost identical to that of the actual intracavernous pressure. The intercept of 6.25 indicates that slight increases in ICP have already occurred when the penile cuff begins to record changes in pressure.

Discussion

The purpose of this investigation was to develop and validate a device to measure intracavernous pressure as an index of penile rigidity. Other devices developed to measure rigidity have used penile stiffness as an index of penile rigidity. Penile

Table 1 Correlation Coefficients between Intracavernous Pressure and Penile Cuff Pressure

Case no.	Correlation coefficients*
1	0.96
2	0.94
3	0.85
4	0.97
5	0.98
6	0.97
7	0.93
8	0.94
9	0.99
Overall	0.96

* $P < 0.001$.

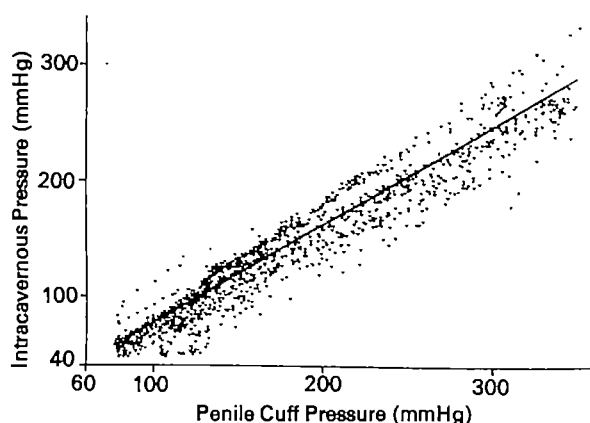


Fig. 3 Scatter diagram and regression line illustrating the highly positive correlation and linear relationship between intracavernous pressure and penile cuff pressure.

stiffness, however, is believed to result from an increase in intracavernous pressure (Lavoisier *et al.*, 1986, 1988a,b; Frohrib *et al.*, 1987). The cuff was therefore designed to estimate ICP in order to assess the physiological event directly responsible for penile rigidity. The cuff was also designed to provide a non-invasive assessment of ICP which is in contrast with the direct but invasive assessment of ICP using implanted needles. The results of this study support its initial goals and show that there is a strong relationship between the penile cuff measure and intracavernous pressure, and that intracavernous pressure can be predicted from the penile cuff. The penile cuff is, therefore, a reliable instrument to estimate ICP and can be used as a valid index of penile rigidity.

Among the latest devices, the Rigiscan (Bradley *et al.*, 1985) has been developed to measure penile rigidity in terms of the mechanical force exhibited by the penis against an external load. This device makes recordings at small intervals but does not provide continuous measurements. Erections of short duration may therefore be missed. This shortcoming may be an important limitation since erections of less than 3 seconds' duration but over 300 mmHg of pressure have been recorded during

nocturnal events (Lavoisier *et al.*, 1988b). The penile cuff device, in contrast to the Rigiscan, allows continuous measurement of penile rigidity, so that erections of very short duration can still be recorded.

Since the penile cuff provides an estimate of ICP, it may become a valuable instrument to assess both tumescence and rigidity. As discussed elsewhere (Lavoisier *et al.*, 1988a,b), the erection process is believed to consist of 2 phases, penile tumescence and penile rigidity, each of which can be described in terms of ICP changes. Tumescence is believed to result primarily from a vascular process whereby the penile cavities fill with blood and the penis becomes distended. This blood inflow triggers increases in intracavernous pressure which can be measured from the penile cuff. Penile rigidity, on the other hand, is believed to result primarily from a muscular process (Lavoisier *et al.*, 1988a,b). At full tumescence, the penile cavities are completely filled with blood and venous outflow is blocked. The penis has therefore become a closed system. Contraction of perineal muscles over this closed system triggers further increases in ICP which exceeds maximal blood pressure and which is thought to be responsible for penile rigidity (Lavoisier *et al.*, 1988a,b). Since the penile cuff estimates changes in ICP, it may estimate the changes occurring during both tumescence and rigidity. The advantage of using the same device for both events is that they would be described along the same continuum and with the same unit of measurement. While validation on normal individuals is still required to determine the ranges of pressure defining tumescence and rigidity, it is believed that these pressure values would show little intersubject variability because internal pressure is independent of penis size. The penile cuff may therefore present advantages over the penile strain gauge by reducing the variability inherent in the strain gauge and by defining each phase of the erection process according to its physiological substrate, intracavernous pressure.

Acknowledgements

The authors thank Mrs Béatrice Michaud for her efficient organisational and administrative work during this research project, which was supported by the Université de Montréal and by Médi-Force Inc.

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Table 2 Statistics and Components of Regression Analysis

Degrees of freedom	1520
Percentage of explained variance	93%
Intercept of the regression line	6.25
Slope of the regression line*	0.84
Standard error of residuals	16.63

*Standard error of the slope of the regression line = 0.006.

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Prompt Orchiectomy Reduces Morbidity and Mortality from Testicular Carcinoma

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Summary—The records of 154 patients with non-seminomatous germ cell testicular tumours were reviewed to determine the potential effect of prompt diagnosis and orchiectomy on morbidity and mortality from this disease. Orchiectomy was performed 30 days or less after the onset of testicular symptoms on 65 patients (Group 1) and more than 30 days after the onset of symptoms on 89 patients (Group 2). The initial clinical stages of Group 1 patients were: I, 40 (62%); II, 14 (22%); III, 5 (8%); marker only, 6 (9%). The initial clinical stages for Group 2 patients were: I, 25 (28%); II, 15 (17%); III, 35 (39%); marker only, 14 (16%). The difference between the percentages of Group 1 and Group 2 patients with stage I disease was statistically significant, as was the difference between the percentages of Group 1 and Group 2 patients with stage III disease. One of the Group 1 patients died, whereas 11 of the Group 2 patients died. In 5 of the Group 2 patients who died, orchiectomy had been performed more than 120 days after the onset of testicular symptoms.

This study suggests that orchiectomy performed promptly after the onset of testicular symptoms not only helps to reduce mortality from testicular cancer but also has a major effect on its morbidity by reducing the need for systemic chemotherapy or major surgery.

During the past 2 decades, progress in surgical technique and the development of effective systemic chemotherapy have dramatically improved the prognosis of patients with non-seminomatous germ cell testicular tumours (NSGCTT). Despite these advances, however, many patients still experience considerable morbidity from treatment and some die of disease.

In general, the morbidity associated with treatment is closely related to clinical stage at presentation. Patients with clinical stage I NSGCTT (cancer confined to the testes) can be treated by orchiectomy initially and then monitored by observation only (the surveillance regimen). Disease recurs in only 30% of these patients, who then require either major surgery or systemic chemotherapy (Peckham and Brada, 1987; Dunphy *et al.*, 1988; Herr *et al.*, 1989; Swanson and Johnson, 1989). By comparison, all patients with clinical stage III disease (dissemi-

nated metastasis) require intensive chemotherapy and some require major surgery as well (Logothetis *et al.*, 1986, 1989a, b; Raghavan *et al.*, 1989). These patients may experience considerable morbidity associated with both major systemic chemotherapy and major surgery.

Mortality from testicular cancer is also closely related to clinical stage. For patients with clinical stage I disease, the cure rate is 98% (Swanson and Johnson, 1989); however, for patients with clinical stage III, it is only 70% (Logothetis *et al.*, 1986).

To determine the potential role of prompt diagnosis and orchiectomy in reducing morbidity and mortality from this disease, we reviewed the records of 154 consecutive patients with NSGCTT who were treated at The University of Texas M.D. Anderson Cancer Center between 1 July 1983 and 31 December 1986.

Patients and Methods

Between 1 June 1983 and 31 December 1986, 172 patients with NSGCTT were evaluated. Complete

information was not available for 13 patients, who were excluded. In addition, 2 paediatric patients and 3 who presented with symptoms of metastatic disease but without testicular signs or symptoms were excluded. Consequently, 154 patients with NSGCTT were included in the study.

For each patient, one of the following subtypes of non-seminomatous or mixed germ cell tumours was histologically confirmed: embryonal carcinoma, endodermal sinus tumour, immature teratoma, mature teratoma, choriocarcinoma, syncytiotrophoblastic giant cells, and seminomatous components. The appropriate pathological material for each case was reviewed by a member of the Pathology Department.

Each patient underwent thorough staging evaluation. This included determination of serum alpha-fetoprotein (AFP) and human chorionic gonadotrophin (HCG) levels by commercially available enzyme immunoassay (Abbott Laboratories, Abbott Park, USA); any values above 5 ng/dl AFP or 3 ng/dl HCG were considered abnormal. Retroperitoneal lymph nodes were evaluated by abdominal and pelvic computed tomography (CT) performed after administering oral and intravenous contrast material. In addition, the patients underwent bipedal lymphangiography according to a technique previously described (Wallace and Jing, 1976), plus a complete physical examination, chest radiography and haematological evaluation (complete blood count and serum multiple analysis).

The tumours were pathologically staged according to the modified Boden and Gibb 1961 staging system as follows: stage I, tumour confined to the testis; stage II, tumour metastatic to regional retroperitoneal lymph nodes; stage III, tumour extending beyond the diaphragm to either mediastinal or supraclavicular lymphatics or generalised visceral or pulmonary metastasis. Most patients with clinical stage I NSGCTT were treated by orchiectomy plus surveillance. Those with no radiographic or clinical evidence of metastasis but with elevated serum tumour markers were considered to have metastatic disease. For the purposes of this review these patients were coded as a separate category (marker only, not stage II).

The clinical records were analysed retrospectively to determine the date of the onset of testicular symptoms and the clinical stage of disease at diagnosis. The symptoms were summarised on the basis of retrospective chart reviews. Testicular symptoms included testicular mass, with or without pain, and pain alone. Three patients who presented

with metastatic disease but no testicular symptoms were not included in this analysis.

Figures 1 and 2 present the probability of diagnosis at stages I and III, respectively, as functions of the delay between the onset of symptoms and treatment. The points at the top and bottom of the figure represent the raw data; a zero value indicates that the patient was not at the stage being considered; a value of 1 indicates that he was.

The wavy dotted lines in the 2 figures represent a smoothing of the raw data. To obtain the probability at each time of delay shown, the proportion of patients in the stage of interest at a time near the particular time was used; this is a form of moving average smoothing. From these smoothed curves it can be seen that the proportion of patients in stage I is about 60% if there is only a small delay between occurrence of symptoms and diagnosis; the proportion decreases with increasing delay and appears to asymptote at about 15% for large delays. The proportion initially diagnosed as stage III is about 10% for small delays and increases roughly linearly at a rate of 8% per month of delay.

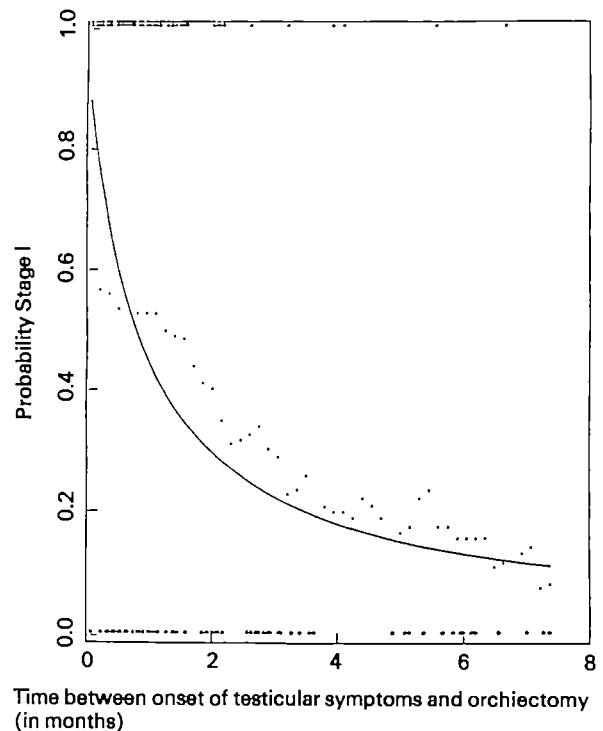


Fig. 1 Probability of clinical stage I non-seminomatous germ cell testicular tumours as a function of the time between the onset of testicular symptoms and orchiectomy. Dots represent results of the moving average technique used to calculate probability. The parametric form is an estimate of the functions shown by the moving average technique (dots).

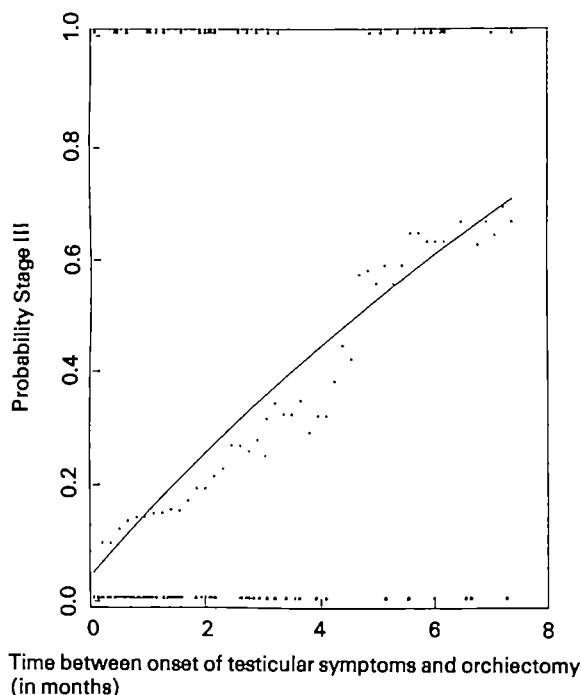


Fig. 2 Probability of clinical stage III non-seminomatous germ cell testicular tumours as a function of the time between the onset of testicular symptoms and orchiectomy. Dots represent results of the moving average technique used to calculate probability. The line is an estimate of the functions shown by the moving average technique (dots).

In order to assess the statistical reality of the apparent changes in probability of diagnosis at a particular stage as related to delay, a simple model was fitted to the data, *i.e.*

$$\text{probability} = \frac{a + b \cdot \text{delay}}{c + \text{delay}}$$

According to this form, the probability begins at one value for zero delay and changes smoothly to a different value for large delays. The rapidity of the change is the third parameter of the model. The solid line in the figures shows the maximum-likelihood fit of this model to the data.

Testing the null hypothesis of no change in proportion to time is equivalent to testing $a=c=0$ in this form. For stage I, the log likelihood ratio for testing this hypothesis was 13.15, yielding a chi-square value of 26.3; the corresponding numbers for stage III were 11.35 and 22.7. In both cases the *P* value was less than 0.001, providing strong evidence that the change in proportion with delay in diagnosis is not due to random fluctuation in the data (Kendall and Stuart, 1979a, b).

Results

The records of 154 patients with NSGCTT were studied. The clinical stages at presentation were: I, 65; II, 29 (excluding marker only); III, 40. In addition, 20 patients had marker elevation only without other clinical evidence of metastatic disease. These patients were included as a separate category.

Orchiectomy was performed 30 days (or less) after the onset of testicular symptoms in 65 patients (Group 1); in 89 patients (Group 2) it was performed more than 30 days after the onset of symptoms. For Group 1 patients the first testicular symptoms were: mass (alone), 36; pain (alone), 6; painful mass, 23. For Group 2 the symptoms were: mass (alone), 52; pain (alone), 6; painful mass, 27; breast tenderness and/or enlargement without testicular symptoms, 4.

The initial clinical stages for Group 1 patients were: I, 40 (62%); II, 14 (22%); III, 5 (8%); marker only, 6 (9%). The initial clinical stages for Group 2 patients were: I, 25 (28%); II, 15 (17%); III, 35 (39%); marker only, 14 (16%). The difference between the percentage of Group 1 patients with stage I disease (62%) and Group 2 patients with stage I disease (28%) was statistically significant ($P < 0.001$). Similarly, the difference between the percentage of Group 1 patients with stage III disease (8%) and Group 2 patients with stage III disease (39%) was also statistically significant ($P < 0.001$).

Probability analysis was used to demonstrate graphically the probability that a patient's disease would be clinical stage I (Fig. 1) or stage III (Fig. 2) as a function of the time interval between the onset of testicular symptoms and orchiectomy. During the period of clinical evaluation (minimum 2-year follow-up), 57% of Group 1 patients required therapy for metastatic disease: chemotherapy only, 32%; chemotherapy plus retroperitoneal lymph node dissection (RLND), 20%; RLND only, 1.5%; chemotherapy plus radiation therapy, 1.5%; treatment unknown, 1.5%. Therapy for metastatic disease was required in 81% of Group 2 patients: chemotherapy only, 55%; chemotherapy plus RLND, 18%; RLND only, 1%; chemotherapy plus radiation therapy, 2%; chemotherapy plus RLND plus irradiation, 1%; treatment unknown, 2%; no treatment, 1%. Metastatic disease did not develop in 43% of the patients in Group 1 and in 19% of those in Group 2 ($P < 0.001$) during the period of follow-up.

One of the 65 Group 1 patients died, whereas 11 of the 89 (12.4%) in Group 2 ($P=0.0072$) died (Fig. 3). Furthermore, 5 of 30 (17%) Group 2 patients who died of testicular cancer were among the 30 who had undergone orchiectomy more than 120 days after the onset of testicular symptoms.

Discussion

Previous investigators have studied how delay in diagnosis affected the clinical stage of testicular cancer in patients who were treated either prior to or at the very beginning of the era of systemic chemotherapy. For example, Bosl *et al.* (1981) examined the effect that delay in diagnosis had on 333 patients with testicular cancer whom they treated between January 1941 and September 1978. The result showed a clear correlation between delay in diagnosis (caused either by the patient or the physician) and clinical stage. The median patient-plus-physician delay for those with clinical stage I disease was 75 days (2.5 months); for stage II, 101 days (3.3 months); for stage III, 134 days (4.4 months).

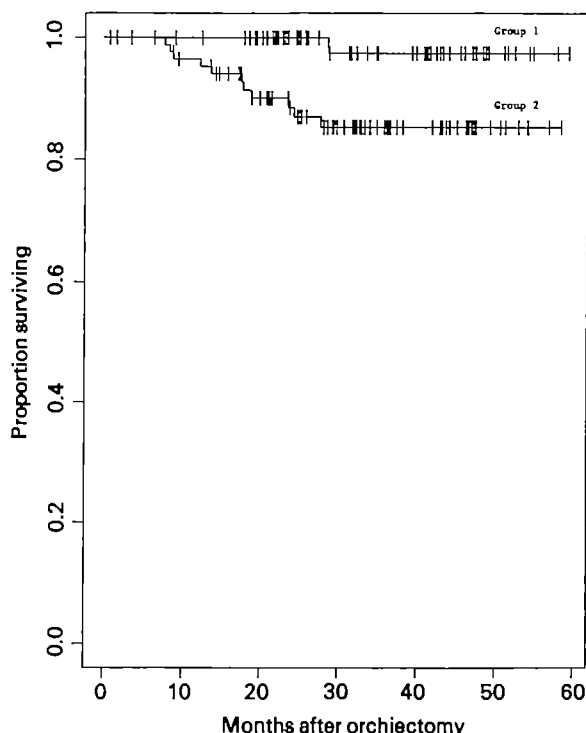


Fig. 3 Crude survival for patients treated by orchiectomy within 1 month after the onset of testicular symptoms (Group 1) compared with the survival of patients treated by orchiectomy more than 1 month after the onset of symptoms (Group 2).

Similarly, Prout and Griffin (1984) studied the influence of delay in diagnosis on the survival of 133 patients treated at the beginning of the era of effective systemic chemotherapy, 1970–1981. They analysed patients with NSGCTT and testicular seminoma separately. Only 4 deaths occurred among 34 patients with NSGCTT who underwent orchiectomy within 1 month of the onset of symptoms, whereas when orchiectomy was delayed more than 1 month, 16 of 55 patients with NSGCTT (29%) died.

Our data confirm and extend these observations. Clinical stage I disease was present more frequently when orchiectomy was performed within 30 days, rather than beyond 30 days, of the onset of testicular symptoms, whereas clinical stage III disease was present more frequently when orchiectomy was performed more than 30 days after the onset of symptoms. Analysis confirmed that the probability of stage I disease decreased significantly with delay between the onset of testicular symptoms and orchiectomy, while the probability of stage III disease increased.

During the period of treatment, 57% of Group 1 patients and 81% of Group 2 patients developed metastasis. Since disease did not metastasise in 43% of Group 1 patients and 19% of Group 2 patients, prompt orchiectomy seemed to reduce the rate of metastasis.

A most important finding was that only 1 patient in Group 1 died, whereas 12.4% of Group 2 patients and 17% of those who underwent orchiectomy more than 120 days after the onset of testicular symptoms died.

Some physicians initially treat suspicious testicular masses with antibiotic therapy. They believe that the mass is properly diagnosed as an infection if it resolves, whereas tumour is more likely if it does not resolve. Our data imply, however, that this treatment policy is dangerous—a testicular tumor may metastasise during the period of antibiotic therapy.

Similarly, our data add a sense of urgency to the evaluation of all patients with suspicious testicular masses. We believe that a definitive diagnosis should be made quickly (using testicular ultrasound when appropriate) and orchiectomy should be performed promptly when it is necessary.

Performing orchiectomy promptly after the onset of testicular symptoms can have a major effect on the morbidity of testicular cancer by reducing the need for systemic chemotherapy or major surgery. Similarly, prompt orchiectomy should reduce the mortality from this disease.

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Microsurgical Vaso-epididymostomy in 2 Layers

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Summary—Eleven patients with epididymal obstruction were treated with microsurgical techniques. A 2-layer, end-to-side anastomosis between the vas deferens and a single loop of the epididymal duct was created. At follow-up, 9 patients had spermatozoa in their ejaculate and 3 of them achieved pregnancies with their partners. The technique described not only yields better results through the application of microsurgery but also gives a better understanding of epididymal function and pre- and per-operative diagnostic proceedings.

Infertility in the male is, in 6 to 7% of cases, caused by obstructive azoospermia, a condition where normally produced spermatozoa cannot reach the ejaculate. The aetiology of this obstruction may be either congenital or acquired. The most common congenital abnormalities of the male ductal system are bilateral insufficiency of the connection between testis and epididymis, a defect of the epididymis or defect of the proximal part of the vas deferens. Absence of the vas deferens may occur unilaterally or bilaterally and may be accompanied by the absence of the seminal vesicles or part of the epididymis (Scorer and Farrington, 1971). Acquired obstruction is more likely to occur within the epididymis. Gonorrhoea, tuberculous epididymitis, non-specific epididymitis and certain surgical procedures (such as the repair of an inguinal hernia or hydrocele of the testis) are known causes of epididymal obstruction.

Since it was first described 80 years ago, the conventional technique of vaso-epididymostomy in the treatment of epididymal obstruction has changed little (Martin *et al.*, 1903). The results are still, in general, less than satisfactory. In the last 10 years, the developments in microsurgery, together with a better understanding of physiological, biochemical and pathological processes in the epididymis, have improved the results of surgical

treatment of obstruction of the epididymis. The reconstructive technique is based on the mobilisation of a carefully isolated single loop of the epididymal duct as caudally as possible and the construction of a 2-layer, side-to-end anastomosis with the vas deferens (Fogdestam *et al.*, 1986; Thomas, 1987).

In order to exclude pre-testicular and testicular causes of azoospermia and to establish the nature of the epididymal obstruction, several criteria have to be met before selecting patients for operative treatment. At physical examination the testis should have a normal volume and the vas deferens should be readily palpable. The endocrinological status of the patient should be normal and the FSH value should not be elevated. Transrectal ultrasound should demonstrate normal, non-dilated seminal vesicles and biopsy of the testis should show normal spermatogenesis.

After acute occlusion of the vas deferens, ruptures in the epididymis are frequently observed in both man and animals. High pressures from a build-up of sperm may occur within the epididymis and can result in small tears of the thin-walled, dilated epididymal tubule. The escape of its contents into the interstitial tissue results in the formation of a foreign body granulomatous reaction around the tubule. This leads to thickening and narrowing with consequent obstruction of the passage of sperm. This has implications for those who request a vasovasostomy after a previous vasectomy (McConnell, 1981; Silber, 1981; Thomas, 1987).

Patients and Methods

In the last 2 years, 14 men with azoospermia were carefully selected and treated with micro-surgical vaso-epididymostomy. Exploration of the scrotum revealed a congenital defect of the cauda epididymidis with a normal vas in 1 patient. Eight patients had an acquired obstruction of the cauda. Five additional patients who requested vasectomy reversal were found to be eligible for vaso-epididymostomy, since exploration of the vas deferens demonstrated bilateral obstruction of the epididymis.

Surgical technique

Under general anaesthesia a vertical incision was made longitudinally on the ventral aspect of the scrotum over the testis. After opening the tunica vaginalis, the entire epididymis was examined. Under the operating microscope an incision was made in the visceral layer of the tunica vaginalis as far distally as possible and a single loop of the epididymal duct was dissected free (Fig. 1). A small window was then cut in the vertex of the dissected loop. If there was a flow from the epididymal duct, a smear sample was spread on a slide and examined under the light microscope. If the smear test was negative, the same procedure was repeated more proximally until patency of the epididymal duct was established. If not, it was concluded that the

occlusion was located at the testicular-epididymal level. The patency of the distal vas deferens was tested by injecting 5 ml of normal saline solution into the open cannulated vas deferens. If the conditions were suitable an end-to-side anastomosis was performed in 2 layers.

Four sutures of 10-0 atraumatic nylon were placed in every quadrant of the opening of the epididymal duct (Fig. 2); they were carried through the mucosa of the vas deferens and tied carefully (Fig. 3).

As a second layer of the anastomosis, the muscularis and adventitia of the vas deferens was sutured to the visceral layer of the tunica vaginalis with 8 9-0 nylon stitches, so as to increase the strength of the anastomosis and prevent leakage of sperm (Fig. 4). In bilateral cases, the mean duration of the procedure was 2.5 h.

This technique could be applied to 10 patients with obstructive azoospermia. Bilateral vaso-epididymostomy was performed in 4 patients and unilateral vaso-epididymostomy in 6. In the last group 2 men had only 1 testicle; in 1 patient the distal vas deferens was obstructed on one side only and in 3 patients the contralateral ductus epididymidis showed absence of spermatozoa up to the caput epididymidis. In 3 patients reconstruction on both sides was not possible as the location of the obstruction was situated on the testicular-epididymal level.



Fig. 1 Microscopic view of dissected loops of the epididymal duct.

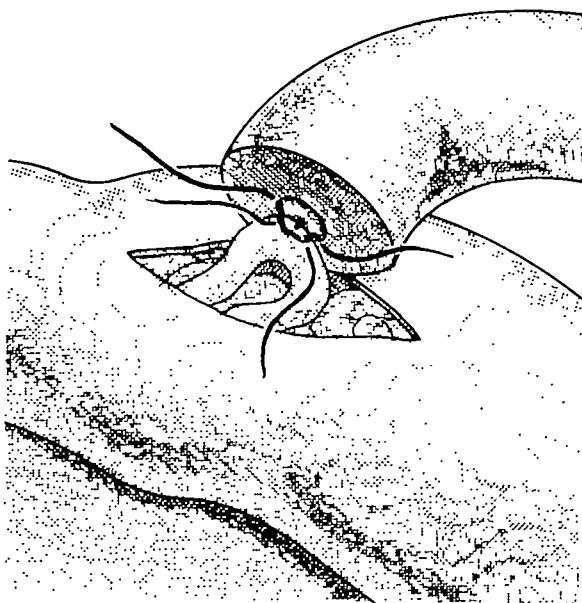


Fig. 2 Diagram of the first layer of the anastomosis.



Fig. 3 Microscopic view of completed first layer of the anastomosis.

Results

There were no complications and all patients left hospital the day after surgery. Sperm controls 3 to 15 months after the vaso-epididymostomy revealed spermatozoa in the ejaculate of 9 patients. In 2

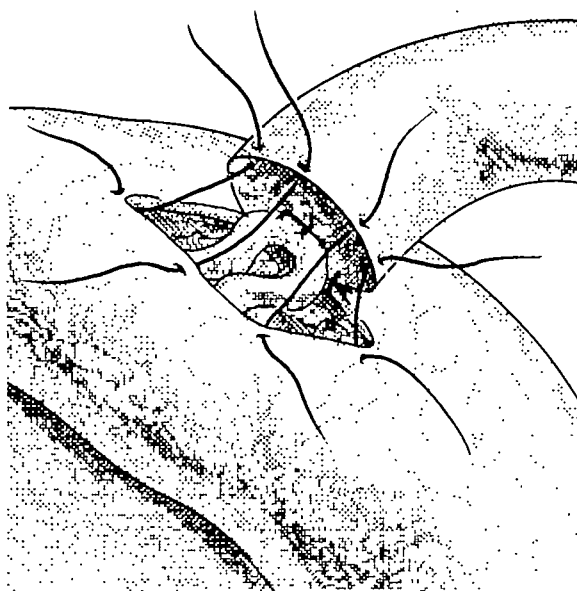


Fig. 4 Diagram of the second layer of the anastomosis.

patients the density of spermatozoa varied between 5 and $20 \times 10^6/\text{ml}$ and in 7 patients the density was higher than $20 \times 10^6/\text{ml}$. Two patients still had azoospermia after 3 to 15 months. In 2 patients the percentage of progressive motility of the spermatozoa was very low and in the remaining 7 the motility was 40% on average. The partners of 3 patients became pregnant 3 to 9 months after surgical treatment (Table).

Discussion

In 70% of patients, the cause of obstructive azoospermia is located in the epididymis. This high percentage is not surprising. The ductus epididymidis can have a length of 6 to 8 m and constitutes an incredibly fine, complex and tortuous system of tubuli with a diameter of 0.2 mm; this is clearly vulnerable during embryonal development and later during infections. In many patients the cause of obstruction remains obscure (Silber, 1981). It is suggested that in some cases a low grade chronic inflammatory epididymitis could be the cause. Other patients may have an initial ischaemic origin as a result of minor trauma or there may be a congenital abnormality within the vasa efferentia (McConnell, 1981).

In addition to the application of continually improved microsurgical techniques, several other factors are important in achieving a successful vaso-epididymostomy. One is the location of the obstruction. It is well known that spermatozoa, while passing through the ductus epididymidis, change morphologically, physiologically and biochemically (Orgebin-Crist, 1981). The results of vaso-epididymostomy improve significantly when the anastomosis is situated at the middle or caudal part of the epididymis rather than at the caput epididymidis (Hendry *et al.*, 1983; Schoysman and Bedford, 1986).

Another determining factor is the presence of serum antisperm antibodies. These antibodies are produced as a consequence of vasectomy or of epididymal duct occlusion. It is widely accepted

Table Results of Microsurgical Vaso-epididymostomy

	Year	No. of patients	Patency (%)	Pregnancies (%)
Fogdestam <i>et al.</i>	1986	41	35 (85)	15 (37)
Thomas	1987	50	33 (66)	18 (42)
Garibyan <i>et al.</i> (present series)	1989	11	9 (81)	3 (27)

that a high antibody titre reduces fertility. Vaso-epididymostomy does not result in a significant reduction of the circulating sperm antibodies (Rumke and Hellinga, 1959; Hendry *et al.*, 1983; Fogdestam *et al.*, 1986).

Over the last 10 years the application of microsurgical vaso-epididymostomy has produced better results than conventional techniques. These successes are not only the result of refined surgical methods but also of better understanding of epididymal function and pre- and per-operative diagnostic proceedings. These enable us to establish more accurate indications for reconstructive surgery in patients with obstructive azoospermia.

The results in this small group of patients, some of whom have not yet been followed up for 6 months, tend to confirm these conclusions.

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PAEDIATRIC UROLOGY

Extracorporeal Shockwave Lithotripsy Monotherapy for Paediatric Urinary Tract Calculi

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Summary—The role of extracorporeal shockwave lithotripsy (ESWL) in the management of paediatric urinary tract calculi was evaluated. The study group included 22 children (13 male, 9 female) with an age range of 2 to 13 years. The renal calculi, including staghorn and ureteric calculi, varied in size from 0.3 to 5 cm. Overall stone clearance at 3 months was 79% with a low incidence of complications (2 children required nephrostomy drainage for sepsis). ESWL is a non-invasive method of managing even complex stones in children of all ages, irrespective of size or position.

Urinary calculi are rare in children, with an estimated 100 new cases per year in the United Kingdom; 85% of stones occur in the kidney and 90% are secondary to infection (Boddy *et al.*, 1987). Innes Williams *et al.* (1982) have stated that there is no place for conservative management of renal calculi in children and stone removal has therefore required surgical intervention including pyelolithotomy, pyelonephrolithotomy or ureterolithotomy. Recent advances in the management of urinary stones, especially percutaneous nephrolithotomy (PCN) and ESWL, may avoid the necessity for open operation (Hulbert *et al.*, 1985). In this study the role of ESWL in the management of urinary tract calculi in children was evaluated.

Patients and Methods

A series of 22 children (13 male, 9 female) was studied over an 18-month period. Their ages ranged from 2 to 13 years (mean 5.8); 7 children were under 3 years of age. Heights varied between 89 and 155 cm (mean 115) and weights between 10 and 52 kg (mean 19.4). Sixteen children presented with urinary tract infections and another 3 had congenital abnormalities. Three children had previously undergone open surgical procedures for the removal of stones. Altogether 24 calculi were

treated, with 2 children having a combination of renal and ureteric calculi. The distribution and size of the stones is shown in Table 1. Renal function was not assessed routinely before and after treatment.

All procedures were performed using a Siemens Lithostar Lithotriptor (Siemens Inc., Erlangen, FRG), a second generation machine using X-ray imaging for stone localisation. Shockwaves generated by an electromagnetic membrane are transmitted to the patient via a gel disk. To ensure co-operation in this young age group all treatments were performed under general anaesthesia including gas inhalation (18 children) or intravenous ketamine (4). Prior to referral for ESWL, 1 child had a percutaneous nephrostomy tube inserted for the relief of obstruction. Nine children were on antibiotics before treatment, or were treated with

Table 1 Distribution and Site of Paediatric Urinary Calculi Treated by ESWL

Location	No.	Size (cm)	Mean size (cm)
Renal			
Staghorn	9	2–5	3.1
Caliceal	5	0.3–1.0	0.6
Pelvic	5	0.5–2.0	1.1
Ureteric			
Upper third	2		
Lower third	3	1.0–3.0	1.6

Accepted for publication 20 October 1989

prophylactic antibiotics on the day after treatment, when abdominal radiographs and ultrasound examination of the kidneys were performed. The success of treatment was judged by the appearance of fragmentation during ESWL and by the level of stone clearance at 3 months.

Results

Twenty-two children with 24 stones required 31 treatment sessions, with 15 children having 1 session, 4 children 2 sessions, and 2 children 4 sessions. All those who required more than 1 treatment had either staghorn or multiple calculi. The generator voltage varied from 16.9 to 19 kV. The number of shocks per patient varied from 1000 to 11,300 (mean 3860). The mean number of shocks for staghorn calculi was 4670, for ureteric calculi 4866 and for renal calculi 3071. Three-month follow-up is complete in 18 children (Table 2): 78% achieved stone-free status with partial clearance observed in an additional 10%. Complications of treatment were uncommon and generally minor. Two children developed a transitory supraventricular tachycardia during treatment. Ventricular ectopics occurred in 1 child but were easily suppressed by cardiac gating of the shockwave rhythm to the normal ECG waveform. Small skin haematomas occurred at the site of shockhead application in almost all children. No abnormality was noted on abdominal radiographs or renal ultrasound; in particular, there was no evidence of perirenal haematoma. In the first 24 h following therapy, 2 patients became pyrexial and required insertion of percutaneous nephrostomy tubes to relieve sepsis obstruction. Only 1 child had subsequent ureteroscopy to remove stone fragments.

Table 2 Three-month Stone clearance after ESWL Monotherapy

Location	No.	Partial clearance (%)	Total Clearance (%)
Renal			
Staghorn	6	1 (16)	4 (67)
Caliceal	4		4 (100)
Pelvic	4	1 (25)	3 (75)
Ureter			
Upper third	2		2 (100)
Lower third	3		2 (66)
All stones	19	2 (10)	14 (78)

Discussion

Extracorporeal shockwave lithotripsy is the treatment of choice for the majority of urinary tract calculi in adults (Kroovand *et al.*, 1987). Technical limitations, including patient size, stone size and location, and concern over the passage of stone fragments, make the role of ESWL in children more difficult to define. Extracorporeal shockwave lithotripsy has 3 clear advantages over open removal of urinary stones (Eisenberger *et al.*, 1985); hospital stay is reduced, the convalescent period is shorter and the complication rate is significantly reduced. Current contraindications to ESWL include obstruction distal to the stone, defects in blood coagulation, acute urinary tract infection and radiolucent calculi (Wilbert *et al.*, 1988).

This series is the largest to date in children of this young age on a second generation X-ray imaging lithotripter. The youngest child was 2 years old and 7 were under 3 years of age, while the mean age was 5.8 years. This contrasts with the 2 previously quoted series by Kroovand *et al.* (1987) and Wilbert *et al.* (1988), where the mean age was 14 years and the youngest child was 6 years old. The present study involved a "true" paediatric population with the oldest child being aged 13 years.

Radiation exposure during ESWL was monitored carefully and, where possible, the gonads were protected with an X-ray shield. It has previously been reported that with a small field, actual radiation exposure during ESWL is smaller than that normally encountered in paediatric abdominal radiography (Kereiakes *et al.*, 1980). Indeed radiation exposure estimated during ESWL is less than for diagnostic radiographic procedures such as barium enema or micturating cystourethrography and is less than that encountered during percutaneous stone manipulation (Bush *et al.*, 1984).

Some investigators have stated that open surgery is still the treatment of choice for large staghorn calculi and that ESWL in paediatric nephrolithiasis should be limited to small stones (Wilbert *et al.*, 1988). In this study, staghorn calculi measuring 4 and 5 cm in diameter were cleared by ESWL without adjuvant therapy. Similarly, previous investigators consider ESWL to be suitable only for upper urinary tract calculi (Kramolowsky *et al.*, 1987), but in the present study 4 of 5 ureteric calculi were cleared completely.

Although small subcutaneous haematomas occurred in many cases, there was a low incidence of significant complications. Only 2 children devel-

oped obstruction requiring nephrostomy and contrary to our experience with adults, we found that children do not routinely require stenting prior to ESWL, even for staghorn calculi. It is difficult to say why this should be. It may sound simplistic, but it is possible that fragmentation was better in this group of patients and so the fragments passed more easily.

Several anaesthetic techniques have been used in the previously quoted series of children undergoing ESWL. These range from general anaesthesia to regional anaesthetic techniques such as epidural analgesia to intravenous sedation. In the present series, general anaesthesia was used to ensure co-operation in these young children.

There was no evidence of macroscopic renal damage immediately after treatment on ultrasound or X-ray examination. Almost all children were referred from other hospitals, being admitted on the evening before or the morning of the procedure and discharged on the following day. Thus it was not possible to examine renal function systematically before ESWL and in the period following treatment.

Long-term follow-up is essential to determine the effects of ESWL on the developing kidney. This is particularly important in children who require multiple treatments. Preliminary reports in children followed for up to 36 months following ESWL show no difference in growth rates between treated and non-treated kidneys, suggesting that renal growth does not appear to be adversely affected (Adams *et al.*, 1989).

In conclusion, ESWL has dramatically changed the treatment of urinary calculi in children. This non-invasive procedure was suitable for stones in all locations irrespective of size. In the present study, stone clearance rates of up to 80% were achieved with minimal morbidity. ESWL may well be the first-line treatment for all paediatric urinary tract calculi, although the long-term effects of lithotripsy on the kidney are unknown. No serious complications have been reported in the first 9 years of treating patients with ESWL, so it is possible to say that it has been shown to be a safe procedure. It must be acknowledged, however, that the effects of ESWL on renal function have not

been critically studied here, but the success rate of treatment was high and the complication rate low.

Acknowledgements

The authors are grateful to Professor B. O'Donnell, Professor E. Guiney, Mr R. Fitzgerald, Professor E. Tempany and Mr D. O'Sullivan for kindly referring the patients.

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Urodynamic Studies in Children who Wet

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Summary—The value of urodynamic evaluation was assessed in children with diurnal and/or nocturnal enuresis without overt obstruction or neuropathy. The hypothesis that children with bladder instability and dysfunctional voiding represent 2 separate populations was also examined.

A simplified urodynamic method was used to evaluate 191 children and they were divided into 3 groups: 64 had normal bladders which were stable during filling and voiding was co-ordinated and complete; 97 had unstable bladders but voiding was normal and co-ordinated; 30 had dyssynergic voiding and an increased volume of residual urine. The urodynamic evaluations were helpful in distinguishing the large number of children with normal findings in whom the problem was motivational. The children with unstable bladders had a physiological abnormality due to delayed maturation and in these cases anticholinergic and musculotrophic agents were usually helpful. The dysfunctional voiders had serious behavioural problems, were difficult to treat, and often required a multidisciplinary approach.

These data indicate that there are indeed 2 distinct groups: 1 with instability alone and 1 with dysfunctional voiding with or without instability. Although infection and/or reflux are common in the former, the more devastating urinary tract changes, particularly heavy trabeculation and elongation of the bladder, occur in the latter group.

Wetting in children in the absence of organic disease, such as obstruction or neuropathy, is a common problem for both parents and paediatricians. The definition of wetting depends on one's viewpoint; 50% of mothers of first-born children expect toilet training to be completed by 16 months (Firman, 1986), but most physicians define loss of urine as abnormal if it occurs regularly after the age of 5. Which children should be referred for a urological examination depends on the presentation. If wetting occurs at night only and/or by day with urgency, motivational counselling, a buzzer alarm and/or pharmacotherapy are often given a trial for 3 months. If these fail, or if the patient has urinary infections or difficulty in voiding at presentation, urological studies should be obtained (Maizels and Rosenbaum, 1985). For these studies, we prefer upper tract imaging with ultrasound and

a simplified form of urodynamics in which filling and voiding fluoroscopy are performed, with bladder pressure monitored during filling.

In these children who fail to respond to standard management, Bauer *et al.* (1980) found that approximately one-third were normal and two-thirds were unstable, and there was a small number of patients with a non-neurogenic neurogenic bladder (Hinman and Bauman, 1973). Bladder instability and non-neurogenic neurogenic bladder are often referred to as if they are at either end of the same spectrum (Allen, 1980; Hanna *et al.*, 1981). The voluntary sphincter contraction that occurs to maintain continence in the face of an unstable contraction was described as dyssynergia or uncoordinated sphincter activity by Koff (1982) and McGuire and Savastano (1984). However, Griffiths and Scholtmeijer (1983) found no relationship between detrusor instability with filling and sphincter overactivity with voiding. The aim of the present study was to test the hypothesis that urodynamic studies are helpful in deciding on management in

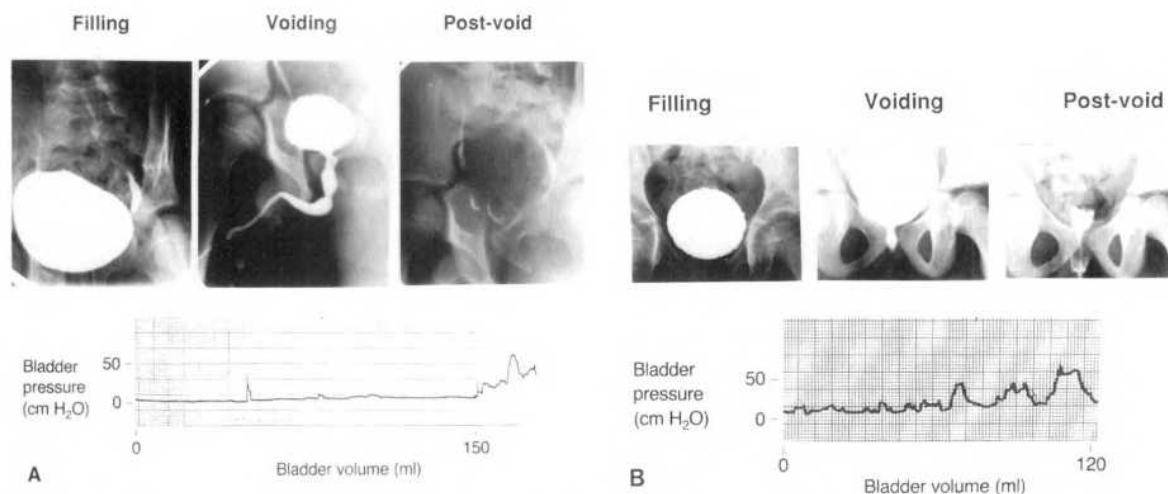


Fig. 1 The X-rays were taken during filling, during voiding and after voiding. The strip chart below the X-rays records bladder pressure and volume during filling only. (A) A 10-year-old boy with an unstable bladder. The bladder wall is non-trabeculated but he has bilateral ureteric reflux. Voiding shows a normal urethra and bladder emptying is complete. (B) This 7-year-old girl has mild trabeculation with detrusor instability. Voiding is normal and complete.

children who wet, and also to show that instability and dysfunctional voiding are 2 distinct conditions and are not at either end of the same spectrum.

Patients and Methods

Children were referred for urodynamic evaluation by other urologists or paediatricians, having failed to respond to routine methods of treatment after a trial of several months. Some were referred before any treatment had been attempted because of obvious complicating factors such as upper tract dilatation, severe reflux, heavy trabeculation or recurrent urinary tract infection (UTI). All had upper tract imaging prior to or at the time of referral. Of the 191 children analysed in this study, 187 had incontinence, 26 had difficulty in voiding as well and 4 had difficulty in voiding but no incontinence. None had obstruction, neuropathy, ectopic ureter or congenital sphincter impairment.

All children were asked to urinate immediately before the urodynamic examination so that an accurate assessment of residual urine could be made. A 2-channel urethral catheter (8, 10, 12 or 14 F, depending on the size of the child) was used and the bladder filled with contrast at 25 to 50 ml/min with the child in the upright position. Bladder pressure was monitored continuously during filling. Fluoroscopy with spot films was performed intermittently every 50 ml or when there was a change in filling pressure due to decreased compliance or unstable contraction. At capacity the catheter was

removed and the child asked to urinate as freely as possible. Fluoroscopy was performed and spot films taken throughout voiding. The results were analysed by means of the χ^2 test with Yates' correction. The definitions of decreased sensation, instability and compliance conform to those of the International Continence Society.

Results

The patients were allocated to 1 of 3 groups according to the urodynamic findings. Normal bladders ($n=64$) were stable with filling and had normal and complete emptying. Unstable bladders ($n=97$) were unstable with filling, but voiding was co-ordinated and an insignificant volume of residual urine (<10 ml) remained. Dysfunctional voiders ($n=30$) had unco-ordinated voiding and/or increased residual urine; 23 (77%) also had instability during filling. All 3 groups were analysed and compared with regard to demographic, symptomatic, radiological and urodynamic factors (Table). In children with normal bladders, UTI (31%) and decreased sensation (34%) were common. This group also contained the largest percentage with daytime wetting alone (31%) or nocturnal enuresis alone (19%), but these did not reach statistical significance. In children with unstable bladders, UTI (45%) was also common and these children had significantly smaller urodynamic bladder capacities, a higher prevalence of decreased sensation (53%), mild trabeculation (24%) and ureteric reflux

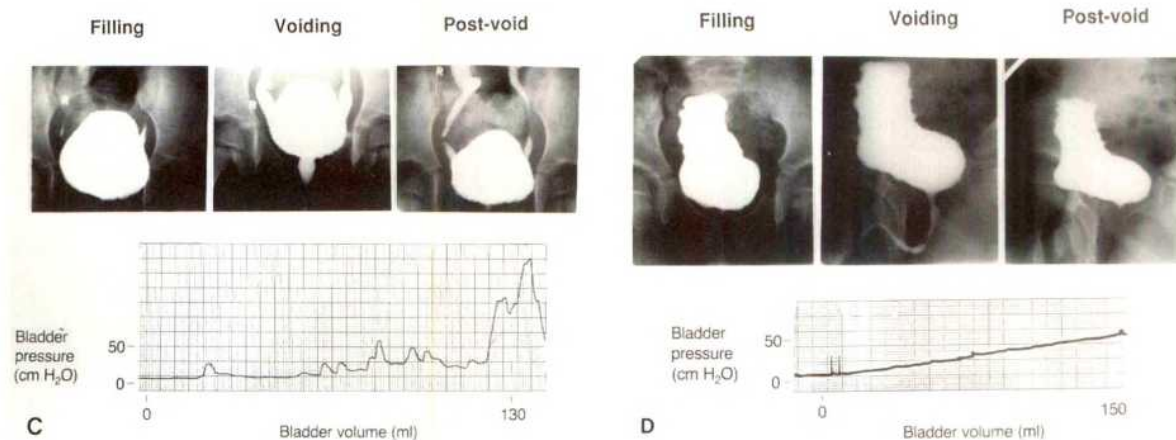


Fig. 1 (Contd.) The X-rays were taken during filling, during voiding and after voiding. The strip chart below the X-rays records bladder pressure and volume during filling only. (C) This 6-year-old girl has mild trabeculation and bilateral reflux which worsens during voiding. The voiding film also shows abrupt cessation of contrast at the distal sphincter and the post-void film shows a large volume of residual urine. Bladder pressure trace during filling shows a very high terminal pressure of 170 cm of water. (D) This boy has a bladder shape and outline similar to that found in a reflex neurogenic bladder. Bladder pressure with filling showed reduced compliance without contractions. Voiding was largely by straining and a normal urethral configuration is shown. There is a large volume of residual urine. This case is an example of a decompensated bladder secondary to long-standing dysfunctional voiding.

(24%) when compared with children with normal bladders. Dysfunctional voiders had a significantly greater prevalence of encopresis (43%), UTI (73%), heavy trabeculation (93%), decreased compliance (27%), elongated bladder outline (63%) and ureteric reflux (50%) than the other 2 groups. The prevalence of decreased sensation (57%) was significantly greater than in the normal bladder group. The volume of post-voiding residual urine was significantly greater in the dysfunctional voiding group because of the way in which this group was defined. It should be noted that the prevalence of high pressure instability (< 50 cm of water) was the same in the unstable and dysfunctional groups. Examples of unstable and dysfunctional bladders and their various stigmata are shown in the Figure.

Discussion

The results of this study were somewhat surprising in that 34% of children had almost normal findings. In addition, 81% of those with normal findings had daytime incontinence, which is so commonly due to instability. If a careful history is taken, the pattern of incontinence is often very erratic, with perfect control at school and wetting at home or vice versa. Also, the history of urgency with squatting or other manoeuvres so often found in the unstable bladder was absent in these children. Management in this group relies on motivational

counselling in which the child learns to take responsibility for the problem, to keep records and to use a programme of timed voidings. It is also stressed to the family that positive reinforcement and not a punitive attitude is essential. If nocturnal enuresis is the chief complaint, the alarm device is worth considering. We have also found that long-term follow-up and encouragement, often by phone with a trained nurse, is very helpful.

As expected, children with unstable bladders formed the largest group and it is well worth making this diagnosis so that anticholinergics (propantheline) and musclotrophic agents (oxybutynin) can be given a good trial before abandoning them. The significantly higher prevalence of ureteric reflux in these patients is also not unexpected and this should resolve with therapy to decrease bladder activity (Koff *et al.*, 1979; Homsey *et al.*, 1985). Mild trabeculation is explained by the fact that these patients are doing extra work against a closed sphincter in between voidings. The 2 patients in this group with heavy trabeculation had previous evidence (difficulty in voiding, increased residual urine and encopresis) that was compatible with a dysfunctional voiding pattern. At the time of evaluation, however, they were voiding and emptying normally. In addition to pharmacotherapy these patients should have the usual motivational counselling, and some may respond well to the alarm for nocturnal enuresis. Some authors advo-

Table Prevalence of Demographic, Symptomatic, Urodynamic and Radiological Features

	Urodynamic categories		
	Normal (n=64)	Unstable (n=97)	Dysfunctional (n=30)
Male (%)	34	44	50
Female (%)	66	56	50
Age (mean $\pm$ SE) (years)	9.92 (0.53)	8.24 (0.34)	8.55 (0.63)
Incontinence (%)			
Day only	31	14	13
Night only	19	2	3
Day and night	50	84	70
Secondary	25	24	43
Stool incontinence (%)	13	9	43 [†]
Urinary tract infection (%)	31	45	73 [†]
Capacity (mean $\pm$ SE) (ml)	245.7 (12.35)	130.8 (7.18) [‡]	205.5 (26.78)
Residual (mean $\pm$ SE) (ml)	4.5 (0.80)	3.6 (0.52)	70.17 (18.95) [‡]
Decreased sensation (%)	34	53 [†]	57 [§]
Mild trabeculation (%)	3	24 [†]	7
Moderate/severe trabeculation (%)	0	2	93 [†]
Unstable detrusor (%)	0	100	77
High pressure (> 50 cm H ₂ O) instability (%)	—	47	43
Decreased compliance (%)	0	0	27 [†]
Elongated bladder (%)	0	0	63 [†]
Ureteric reflux (%)	8	24 [†]	50 [†]

* = 14% (4 children) had no incontinence.

† = Significant difference ($P < 0.05$) between unstable and normal.

‡ = Significant difference ($P < 0.05$) between unstable and both normal and dysfunctional.

§ = Significant difference ($P < 0.05$) between dysfunctional and normal.

† = Significant difference ($P < 0.05$) between dysfunctional and both normal and unstable.

cate bladder exercises, including stopping the urinary stream while voiding (Schmitt, 1982). This seems undesirable in view of the risk of encouraging a dysfunctional voiding pattern. Dysfunctional voiders are distinguished by severe bladder wall changes. Many also have encopresis and decreased compliance, both of which are much less common in the other 2 groups. Management is very difficult and should include a multidisciplinary approach, with psychosocial evaluation and counselling, regulation of constipation and encopresis, and often intermittent catheterisation, anticholinergics, antispasmodics, antibiotics, and biofeedback to retrain the child in normal pelvic floor relaxation (Hinman and Bauman, 1973; Allen and Bright, 1978; Maizels *et al.*, 1983).

Our findings support those of Griffiths and Scholtmeijer (1983) that there was no association between urethral overactivity during voiding and detrusor activity during filling. The severe bladder wall changes were almost confined to the dysfunctional voiding group, and other evidence of pelvic floor dysfunction (encopresis) was also much commoner in these children. Contraction of the voluntary sphincter to prevent incontinence during an unstable contraction is a normal response and

should not be called dyssynergia (Koff, 1982; McGuire and Savastano, 1984) or "voiding problem" (Bauer *et al.*, 1980). In one of his original reports on this subject, Hinman (1980) categorised patients with instability (failure to inhibit) separately from those with dysfunctional voiding (failure to co-ordinate) and those with "lazy bladders" (excessive inhibition). However, in a later review he grouped them together (Hinman, 1986), regarding them as part of the same spectrum. Learning toilet training may involve voluntary contraction of the pelvic floor sphincter against an unstable bladder contraction, but this should not affect the voiding phase. Also, dysfunctional voiding may begin after the completion of normal toilet training, and we found that secondary incontinence was more common in dysfunctional voiders (43%) than in the other 2 groups (approximately 25%), but this difference was not statistically significant. The difference in the bladder wall changes in dysfunctional voiders cannot be ascribed to the height of the pressure generated by unstable bladder contractions, as these were comparable in those who had instability alone and, in addition, 23% of dysfunctional voiders did not have instability. It seems that interruption of voiding by sphincter overactivity is

much more harmful to the bladder than unstable contractions during filling, presumably on the basis of higher pressures generated by the sudden cessation of voiding. In the present study voiding pressures were not measured, and in the literature on dysfunctional voiding the raw data on the height of maximum isometric contractions during voiding are not given (Allen and Bright, 1978; Griffiths and Scholtmeijer, 1983; Webster *et al.*, 1984). Although bladder instability has potentially serious consequences due to infection and reflux, the devastating changes occur with dysfunctional voiding, and putting all of these in the same category may lead to over-treatment of one group or undertreatment of the other.

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Endoscopic Correction of Vesicoureteric Reflux in Children with Spina Bifida

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Summary—Twenty patients with vesicoureteric reflux (VUR) secondary to a neuropathic bladder and associated spina bifida were treated with the endoscopic injection of subureteric polytetrafluoroethylene (Teflon) paste. Of the 19 patients (29 ureters) followed up, 13 have persistent reflux, although only 3 of these ureters have needed a second injection. Twelve of the 16, where reflux resolved, required only 1 injection.

Vesicoureteric reflux is difficult to manage in patients with a neuropathic bladder, particularly as the reflux rarely resolves spontaneously and may even become worse (Diamond and Boston, 1987). Also, ureteric reimplantation is more difficult in these thick walled, trabeculated bladders and antibiotic prophylaxis is hampered by a high incidence of resistant organisms. Submucous Teflon injection (STING) has previously been shown to resolve both primary reflux (Puri and O'Donnell, 1987; Schulman *et al.*, 1987; King and Gollow, 1988) and reflux from neuropathic bladders (Puri and Guiney, 1986; Quinn *et al.*, 1988).

In order to reassess the value of this technique in spina bifida patients we reviewed the results from a group of 20 patients, all of whom had the same neuropathic aetiology and whose endoscopic procedures were performed by the same surgeon (E.J.G.).

Patients and Methods

Twenty patients (16 female and 4 male) with VUR secondary to spina bifida-related neuropathic bladder were included in the study. Their average age at the time of the first STING was 55 months (range 7–179). Reflux was unilateral in 9 and bilateral in

11. None had duplex ureters. Of the 31 refluxing units, 29 have had at least one follow-up micturition cystourethrogram (MCU). Table 1 shows the initial reflux grade in those 29 kidneys. VUR was treated if the patient had grades III, IV or V disease, together with upper tract deterioration or multiple recurrent urinary tract infections. Grade I reflux was treated in 1 patient where a higher grade was present on the contralateral side. Persistent reflux was treated on 7 occasions.

All patients were treated between 1984 and February 1989 and some early patients had an MCU on the first post-operative day. This practice has been replaced by the policy of performing an MCU and ultrasound (US) at 3 months and an MCU and an intravenous urogram (IVU) at 12 months. Patients are usually discharged on the same day and maintained on antibiotic prophylaxis for 2 weeks.

Teflon was injected using the 11.5F Wolf "Stinger" via a rigid needle with a 20G tip, either 0.9 or 1.4 mm in length. A detailed description of the technique is given by O'Donnell and Puri (1988). Whenever a ureteric orifice was difficult to see, a ureteric catheter was inserted to aid visualisation of the effect of injection in more irregular, inflamed bladders.

Reflux grades were assessed using "five" grade system of the International Reflux Committee Report (1981).

Results

Complete resolution of reflux occurred in 16 of 29 ureters. Of the 16 ureters, 12 had an MCU at least 12-months after their last Teflon injection, 5 of these being carried out after 18 months. Table 1 shows the reflux grades for those ureters where reflux was either resolved by the STING or where reflux persisted. Five of 7 ureters with grade V reflux ceased refluxing (Fig. 1) but, 9 of 15 grade IV refluxing ureters had persistent reflux, 3 of which were subsequently recorded as grade V reflux. Figure 2 indicates the grade changes in those ureters with persistent reflux.

The number of Teflon injections required to achieve cessation of reflux is shown in Table 2.

Table 1 Original Reflux Grade and Results in 29 Ureters after STING

Grade	Resolved reflux No. of ureters	Persistent reflux No. of ureters	Total
I	1	0	1
II	0	0	0
III	4	2	6
IV	6	9	15
V	5	2	7
	16	13	29

Table 2 Number of Injections of Teflon per Ureter (STING) for those with Resolved and Persistent Reflux

No. of STINGS/ ureter	Resolved reflux No. of ureters	Persistent reflux No. of ureters	Total no. of ureters
1	12	10	22
2	3	3	6
3	1	0	1
	16	13	29

Twelve ureters received 1 STING and only 1 ureter needed 3 injections before reflux resolved. At present, half of those that underwent a second STING no longer reflux.

No reimplants were performed in this group and none of the 29 ureters were obstructed. A number of other features are relevant to these patients; 2 had aborted attempts at Teflon injection as their bladders were markedly oedematous and inflamed on cystoscopic examination. On 4 occasions reflux recurred after treatment was initially successful—all of the initial MCUs were performed 1 day after the STING; 1 patient showed no change in grade V reflux after 1 STING but spontaneously improved to grade II disease.

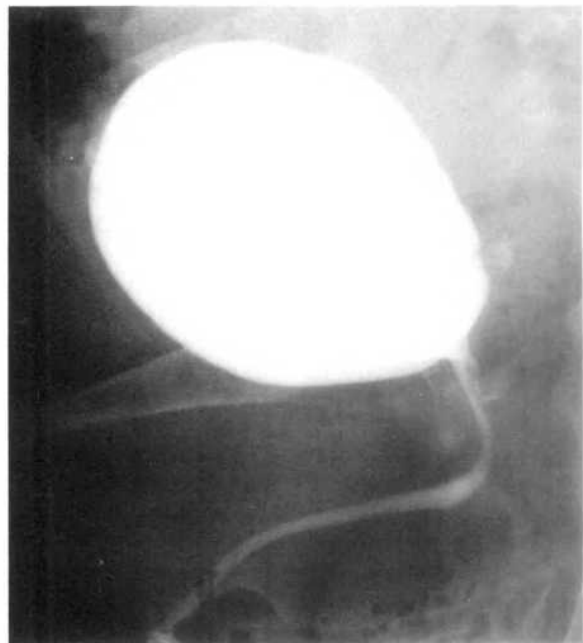


Fig. 1 (A) Bilateral grade V reflux in a 6-month-old boy. (B) MCU 2 months after 0.5 ml of paste injected below each ureter. No reflux was seen at 14 months or 26 months after STING.

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Primary Realignment of Posterior Urethral Ruptures in Children

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Summary—Primary realignment was used in the treatment of 12 children with complete rupture of the posterior urethra; 10 developed strictures but 7 of these responded to dilatation. Problems of continence were encountered only in patients who developed strictures. Since primary realignment results in dilatable strictures in most patients, it is suggested that this should be the treatment of choice in children.

Due to the flexibility of the pelvis, posterior urethral injuries are less common in children and most of the experience in treating these injuries has been gained in adult patients (Reichard *et al.*, 1980).

Two methods are currently used:

- a) Suprapubic cystostomy immediately after trauma followed by repair of the posterior urethral stricture.
- b) Suprapubic cystostomy plus urethral realignment over an indwelling urethral catheter with or without suture anastomosis as an initial procedure (Waterhouse and Gross, 1968; DeWeerd, 1977; Morehouse and MacKinnon, 1980).

Both methods have given satisfactory results, but most of the patients have been adults and experience in children is limited. A retrospective clinical study was therefore carried out to evaluate the results of primary urethral realignment in children.

Patients and Methods

Over an 8-year period, from 1979 to 1987, 12 children were diagnosed as having complete posterior urethral ruptures. There were 11 males and 1 female aged between 2 and 15 years (mean age 8 ± 2.99 years).

The causes of injury were road traffic accidents

(7 patients), falls (4) and penetrating pelvic injury (1). Ten patients also had accompanying pelvic fractures.

The diagnosis of posterior urethral rupture was established by retrograde urethrography. Following initial resuscitation (maintenance of adequate pulmonary function, restoration of blood volume, etc), the patients were operated on through Pfannenstiel incisions. A vertical cystotomy was performed and the internal urethral meatus was exposed. A size 26 Walter's paediatric urethral bougie was passed through the internal urethral meatus up to the rupture. A Foley urethral catheter of appropriate size (10–16 F) was inserted through the external urethral meatus to the rupture. The tips of the bougie and catheter were in the retropubic region and a 2/0 silk suture was placed at the tip of the catheter. The other end of the suture was tied to the bougie and this, together with the catheter, was drawn into the bladder. The silk suture was then removed. The balloon of the catheter was filled with physiological saline and the bladder was repositioned without performing suture anastomosis. Cystostomy was performed by inserting a Malecot catheter, size 22 or 24. The tips of the Malecot and Foley catheters were sutured with 2/0 chromic catgut to prevent accidental removal. The bladder was closed in 2 layers and a perivesical Penrose drain was inserted.

The urethral catheter remained *in situ* for 4 weeks. It was then withdrawn and an anterior

urethrogram obtained via the cystostomy. If the urethral calibre was adequate, the cystostomy tube was closed and the patient's micturition was observed. If this was normal and there was no residual urine, the cystostomy tube was removed and spontaneous closure was allowed to take place.

If the urethral stricture was diagnosed during antegrade urethrography, urethral dilatations were initiated. After the initial dilatation the cystostomy tube was closed but left in place. Micturition and post-voiding residual urine were observed. The cystostomy tube was removed when micturition was normal and there was no residual urine.

The dilatations were carried out weekly during the first month, once every 2 weeks during the second month and monthly thereafter. Urethrography was carried out as required. All patients were followed up for at least 2 years. Early post-operative complications, stricture and continence were evaluated. Strictures which required less than 4 dilatations were classified as mild; those which required 5 to 11 dilatations were regarded as moderate and those requiring more than 12 dilatations were considered persistent. In the latter case urethroplasty was performed.

Results

The ruptures were all found to be complete and no complications were encountered during surgery or in the early post-operative period. Late complications included mild strictures in 2 patients and moderate strictures in 5. There was no tendency towards aggressive stricture formation in these patients and the strictures were relieved by dilatation. Three patients had persistent strictures. Nine were continent, 1 had nocturnal enuresis and 2 were incontinent. Other complications included prolonged urinary tract infection in 3 patients (treated by antibiotics) and bladder calculi in 1 patient, which required surgical removal. The mean duration of follow-up was 5.83 ± 2.04 years (Table).

Discussion

The criteria for successful management of posterior urethral ruptures are a satisfactory urinary stream without stricture, no urinary infection, urinary continence and sexual potency.

To meet these criteria, immediate realignment or initial cystostomy plus treatment of the stricture

Table Results of Treatment

Patient no.	Age Sex	Trauma	Associated pelvic injury	Follow-up (years)	Continence	Stricture	Prolonged infection	Other complications
1	14 ♂	P	—	10	+	—	—	—
2	3 ♀	RTA	Right-sided ischium and pubic fractures	7	+	Moderate	+	Bladder calculi
3	15 ♂	RTA	Right-sided inferior pubic ramus fracture	2	+	Moderate	+	—
4	15 ♂	RTA	Bilateral pubic and left-sided ischium fractures	11	+	Mild	—	—
5	2 ♂	F	—	9	+	—	—	—
6	11 ♂	RTA	Left-sided ischium, superior and inferior pubic ramus fractures	7	+	Moderate	+	—
7	7 ♂	F	Right-sided pubic ramus fracture	7	+	Moderate	—	—
8	8 ♂	F	Right-sided ischium and pubic fracture	6	Nocturnal enuresis	Persistent	—	—
9	6 ♂	RTA	Superior and inferior pubic ramus fracture on each side	4	Incontinent	Persistent	—	—
10	3 ♂	F	Right-sided ischium and pubic fracture	2	+	Mild	—	—
11	5 ♂	RTA	Right sided ischium and pubic fracture	3	Incontinent	Persistent	—	—
12	7 ♂	RTA	Right-sided ischium and pubic fracture	2	+	Moderate	—	—

RTA: Traffic accident. F: Fall. P: Penetrating injury.

have both been used. The advocates of initial cystostomy plus treatment of the stricture claim that open exploration and immediate realignment may damage the nerves and blood vessels which supply the bladder neck and genitalia. The surgical intervention itself rather than the initial injury, may cause major complications and initial cystostomy prevents such complications (Morehouse *et al.*, 1972). Cystostomy, however, results in strictures which are difficult to treat in children (Gonzales and Guerriero, 1985).

According to the supporters of primary realignment, immediate suprapubic exploration and realignment of the torn urethral ends over a catheter is a safe procedure which achieves satisfactory results. They believe that impotence and incontinence are related to the initial injury and if early realignment and correct positioning are not achieved, extensive and difficult strictures may result (Blandy, 1975; Glass *et al.*, 1978; Patterson *et al.*, 1983).

In the present series, 10 of 12 patients had strictures, but 7 responded to dilatation. Problems with continence were found only with persistent strictures. Although 2 of our patients were totally incontinent, 1 had nocturnal enuresis only. Other complications, such as prolonged urinary infection in 3 patients and bladder calculi in 1, may not be consequences of primary realignment but may also be encountered after other methods of treatment. Since most of our patients were prepubertal, we have not been able to evaluate their sexual potency.

Malek *et al.* (1977) reported 3 strictures that responded to dilatation and 1 that required surgical intervention (with no potency or continence problems) following primary realignment in 7 children. De Weerd (1977) also reported successful results in 7 children treated by primary realignment. Since this procedure has been reported to yield less satisfactory results in adults, with 50 to 100% developing strictures, 50% being impotent and 33 to 66% being incontinent (Wilkinson, 1961; Pierce, 1972), the successful outcome among children might result from their capacity to heal (Malek *et al.*, 1977). In addition, realignment over a catheter with no attempt at suture anastomosis might have prevented further trauma, which is reported to be

a factor that affects the outcome (Mitchell, 1968; Morehouse *et al.*, 1972). It also resulted in strictures that responded to dilatation.

Primary realignment over an indwelling catheter, with no suture anastomosis, produced satisfactory results in this series and should be considered an alternative treatment for posterior urethral rupture in children.

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Case Reports

Stress Incontinence due to Pelvic Floor Muscle Involvement in Limb-girdle Muscular Dystrophy

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Limb-girdle muscular dystrophy encompasses a spectrum of disorders involving a number of different muscle groups (Kazakov *et al.*, 1974). Little attention has been paid to involvement of the pelvic floor musculature in this syndrome. We describe a patient with this condition who originally presented with stress incontinence at 12 years of age.

Case Report

A 48-year-old nulliparous woman presented with incontinence of urine. This began at 12 years of age on jumping and deteriorated until it was also present on coughing and walking. Lower limb weakness developed at 33 years of age, when limb-girdle muscular dystrophy was diagnosed. This progressed to involve upper and lower limbs proximally and girdle muscles, causing weakness and

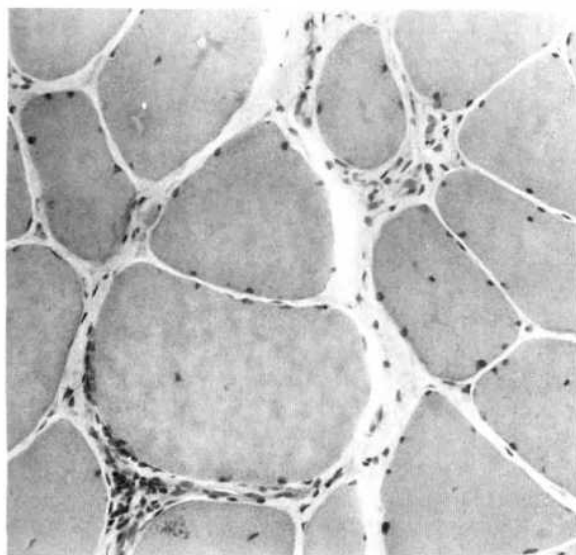


Fig. 1 Mixed hypertrophy and atrophy of the muscle fibres with many fibres having internal nuclei (H and E $\times 200$).

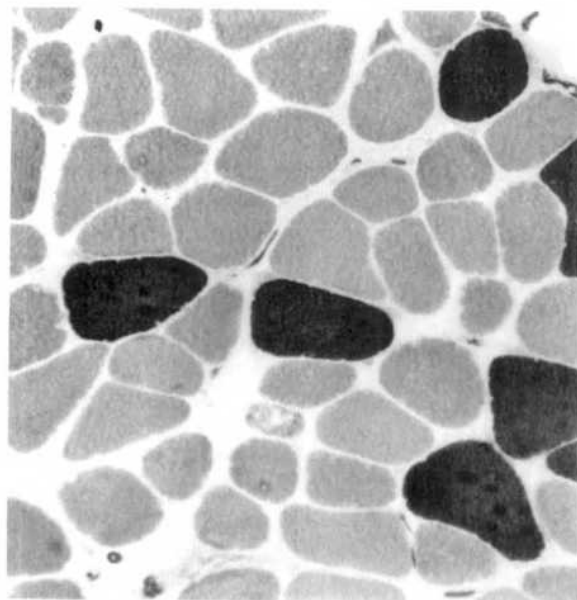


Fig. 2 Myosin ATPase reaction showing predominance of type I fibres ($\times 150$).

wasting. The serum creatine kinase was 197 iu/l (normal 24–170 iu/l). Concentric needle electromyography (CNE) of tibial and supraspinatus muscles showed short duration polyphasic units with an excessively full interference pattern, characteristic of this disorder. Videocystometry demonstrated marked bladder base descent and stress incontinence with no detrusor instability. Urethral sphincter CNE was normal. A vagino-obturator shelf repositioning was performed and biopsies were taken from the pelvic floor muscles. Histologically these showed hypertrophy and atrophy of muscle fibres with about 40% of fibres having 1 or more internal nuclei (Fig. 1). Fibre splitting and a few bizarre and whorled fibre forms were seen. Acid phosphatase activity was increased and the myosin ATPase reaction showed a predominance of type I fibres (Fig. 2). NAD tetrazolium reductase staining demonstrated disruption of the myofibrillar pattern. These histological changes were consistent with a diagnosis of limb-girdle muscular dystrophy (Nemir and Middleton, 1954). The patient progressed well post-operatively and was free of stress incontinence 6 months later.

Comment

If stress incontinence presents at an early age, it is likely to be related to muscular dystrophy. Although rare before childbearing, stress incontinence can occur at any age (Snooks *et al.*, 1985). Much debate has taken place over the relative importance of bladder neck and urethral sphincter mechanisms in these patients, and it is recognised that loss of

normal urethrovesical positioning will also predispose to stress incontinence (Weller, 1984). CNE demonstrated no evidence of urethral sphincter dysfunction and this lady was nulliparous. This case lends support to the suggestion that abnormal positioning of the vesicourethral junction is an important contributory factor in the genesis of stress incontinence.

Acknowledgement

We thank Dr J. Round for histological studies of the muscle biopsies.

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Requests for reprints to: P. J. Dixon, Department of Obstetrics and Gynaecology, Queen Charlotte's Hospital, Goldhawk Road, London W6 0XG.

Unilateral Intra-abdominal Testis with Seminoma in a Previously Unrecognised Hermaphrodite

A. GÜRSAN and A. N. EĞİLMEZ, *Department Of Urology, University Hospital, Ege University, Izmir, Turkey*

Case Report

A 31-year-old infertile man, married for 6 years, complained of painful bilateral gynaecomastia. Examination revealed 1 hypoplastic testis with a small hydrocele. Both breasts were swollen and painful (Fig.). Blood and urine, tumour markers AFP, β -HCG, CEA and testosterone, and X-ray of the chest were all normal. However, the FSH was 48 mIU/ml (normal 2–15), LH was 52 mIU/ml (normal 5–20) and oestradiol was 132 pg/ml (normal 6–44). A spermogram revealed azoospermia. Ultrasonography and CT scanning revealed a 3 × 5 cm solid soft tissue mass behind and above the bladder.



Fig.

A biopsy was taken from the left testis. At laparotomy we found, close to the entrance of the right inguinal canal, a hard malignant testis and 5 hard nodules 1 cm in diameter in the surrounding tissue. There was another 3 × 5 cm mass behind the right side of the bladder adherent to the tumour.

Histological examination revealed that in the biopsy from the left testis there was only atrophic tissue, with no spermiogenesis. In the excised right testis and in the hard nodules in the surrounding tissue there was a typically pure seminoma. The testicular tissue from the tumour was atrophic. The mass excised from behind the bladder was an atrophic uterus. Post-operative recovery was unremarkable. Determination of the sex chromatin from the buccal mucosa was negative. The karyotype was 46 XY.

One week after the operation the oestradiol was normal. The pelvic and para-aortic zones were irradiated with a total dose of 3600 cGy and after 2 weeks the mediastinal and supraclavicular zones were irradiated with a total dose of 3000 cGy.

Comment

In the literature we found 9 cases of pseudohermaphroditism with bilateral testicular tumours and 1 case of hermaphroditism with bilateral intra-abdominal testes and seminoma (Gilbert, 1942; Raines and Hurdle, 1955; Kaisary and Williams, 1982).

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Requests for reprints to: A. N. Egilmez, Department of Urology, Ege Universitesi Hastanesi, Bornova, 35000 Izmir, Turkey.

Granulocytic Sarcoma (Chloroma) of the Kidney and Prostate

Y. F. CHAN, *Clinical Pathology Unit, Princess Margaret Hospital, Hong Kong*

Case Report

A 79-year-old Chinese man was admitted for investigation of anaemia. He also had symptoms of prostatism. On admission he was pale but afebrile and was not jaundiced. There was no lymphadenopathy and the liver, spleen and kidneys were not palpable. Per-rectal examination showed prostatic enlargement. Chest X-ray was normal. Blood tests showed a low haemoglobin level of 8.5 g/dl, white cell count of $2.15 \times 10^9/l$ with normal differential and platelet count of $183 \times 10^9/l$. Blast cells were not found. Other laboratory investigations were normal except for a slightly elevated serum alkaline phosphatase level. Marrow trephine biopsy disclosed a reduced number of mature granulocytes but no leukaemic or malignant cells. KUB showed normal renal shadows and prostatic calcifications. Cystoscopy and intravenous urography provided no additional findings. Computed tomography of the abdomen revealed no abnormal masses. Eventually transurethral resection (TUR) of the prostate was performed but the patient died soon after the operation. Post mortem examination showed enlarged kidneys with an ill-defined green lesion in the right. The liver and spleen were not enlarged. Microscopically the renal lesion showed dense interstitial infiltration of immature granulocytic cells (Fig. 1), some of which were recognised to be eosinophilic myelocytes (Fig. 2). They were positive for both chloroacetate esterase (CAE) and anti-lysozyme immunoperoxidase stains. Large aggregates of similar cells were found in the prostate and a diffuse infiltrate of immature granulocytes was also present in the liver, spleen and bone marrow but no circumscribed lesions were noted.

Comment

Granulocytic sarcoma is a localised tumour mass composed of immature cells of the granulocytic series (Rappaport, 1966). It occurs in 3 clinical settings: as a forerunner of acute myeloid leukaemia

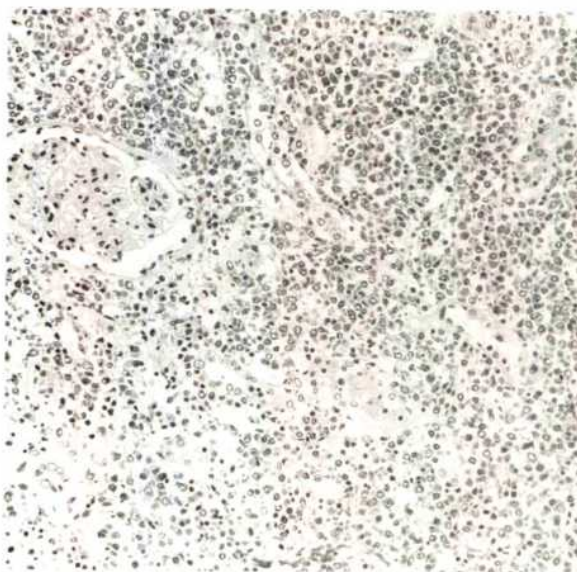


Fig. 1 Section of the kidney showing massive infiltration by immature granulocytic cells. (H and E $\times 100$).

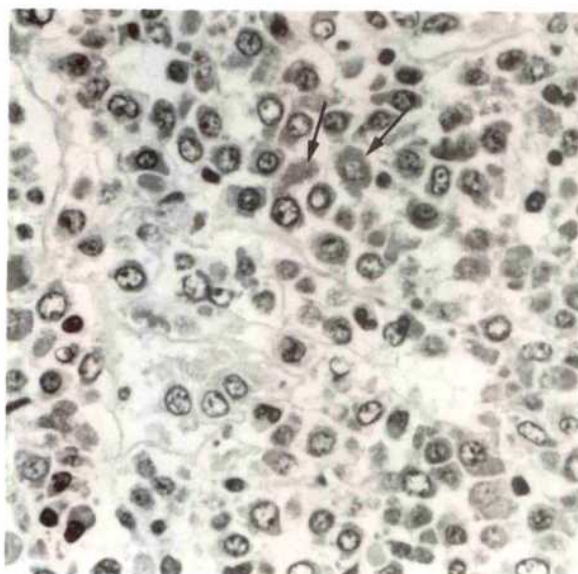


Fig. 2 Higher magnification of the immature granulocytic cells. Note eosinophilic myelocytes with distinct cytoplasmic granules (arrows). (H and E $\times 500$).

(AML) in non-leukaemic patients, as a sign of impending blast crisis in chronic myeloid leukaemia or leukaemic transformation in myelodysplastic disorders, and as a tissue manifestation in patients with established AML (Neiman *et al.*, 1981). The lesion is most commonly found in bones, periosteum, lymph nodes, skin and epidural structures and has also been reported in numerous other sites

such as the female genital tract, gonads, breast, gastrointestinal tract and urinary bladder. Simultaneous involvement of the kidney and prostate is rare. Clinical manifestations are highly variable and symptoms are dependent on local destructive or compressive effects of the mass. Tumours localised primarily in the viscera often remain asymptomatic and are only found incidentally at autopsy. This case was unique in that the diagnosis could have been made, albeit fortuitously, by examination of the TUR specimen of the prostate.

Histologically the lesion has often been wrongly interpreted as malignant lymphoma, resulting in the administration of inappropriate treatment (Meis *et al.*, 1986). Recognition of granulocytic differentiation in the form of eosinophilic myelocytes with either positive CAE or anti-lysozyme immunoperoxidase stain in the immature cells is mandatory to establish the diagnosis.

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Requests for reprints to: Y. F. Chan, (Fetal and Infant Pathology), Institute of Child Health, Royal Liverpool Children's Hospital, Alder Hey, Eaton Road, Liverpool L12 2AP.

Acute Retention Followed by Unexplained Intractable Contraction of the Bladder

R. M. KERNOHAN and S. R. JOHNSTON, *Department of Urology, Belfast City Hospital, Belfast*

Case Report

A 54-year-old male, maturity onset diabetic was referred with chronic retention of urine. He complained of a 5-year history of recurring dysuria and frequency which responded to antibiotics. He had had a single episode of haematuria 4 months prior to consultation and had hourly frequency and nocturia with a slow intermittent stream. Examination revealed a distended bladder containing at least 700 ml of urine. An intravenous urogram confirmed the distended bladder with normal upper tracts and a

neural arch defect consistent with spina bifida occulta. There was no neurological deficit. Rectal examination revealed a small benign prostate. The patient refused transurethral resection and he was started on phenoxybenzamine; this made him incontinent at night and it was therefore stopped. Two days later he developed acute retention and catheterisation produced 850 ml of urine. Urea was 17.0 mmol/l falling to 5.4 mmol/l after 5 days.

Cystourethroscopy was performed 14 days later. The urethra was normal to the verumontanum and the prostate did not appear occlusive, but the bladder was so contracted that the urethra appeared to end blindly at the level of the bladder neck. The bladder could not be distended hydrostatically and a suprapubic catheter was inserted through an open incision. Biopsy of the bladder wall showed non-specific inflammation with minimal chronic infiltrate in the lamina propria. An ascending urethrogram demonstrated a thimble-sized bladder with bilateral ureteric reflux (Fig.). The suprapubic catheter was left *in situ* and a further cystourethroscopy 5 months later revealed a bladder capacity of 30 ml and normal ureteric orifices. The suprapubic catheter was replaced by a urethral catheter. This was removed after 1 month, when he was able to pass water satisfactorily, but he had intense frequency due to the small bladder capacity. An ultrasound scan of the kidneys and an IVU demonstrated bilateral hydronephrosis and the urethral catheter was replaced. Follow-up ultrasound 4 months later demonstrated that the upper tracts had returned to normal. Currently he remains with a urethral catheter.

Comment

The chronic retention and the episode of acute



Fig. Cystogram demonstrating small bladder with bilateral ureteric reflux.

retention cannot be explained by evidence of outlet obstruction. Histology of the detrusor muscle was unhelpful. The chance finding of spina bifida occulta and the fact that the patient is diabetic may mean that there is a neurogenic cause for the bladder behaviour, although we have been unable to demonstrate any other evidence of neurological disease. If the distal sphincter tone was very high initially, this could explain the retention with a high bladder pressure, reflex contraction of the bladder occurring when catheter drainage was instituted. However, following removal of his catheter he had incontinence with a persistently shrunken bladder and developed bilateral ureteric reflux with upper tract dilatation which would not support this hypothesis. Cases are reported in the literature of accidental infusion of vinegar and Dettol (Kinder, 1959) and Bonney's Blue (Christmas *et al.*, 1989) into the bladder causing reduction of bladder capacity, but there was no evidence that a foreign substance had been administered to our patient.

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Requests for reprints to: R. M. Kernohan, Department of Urology, St Peter's Hospital, Henrietta Street, London WC2E 8NE.

Bleeding following Percutaneous Nephrolithotomy resulting in Loss of the Kidney

R. M. KERNOHAN, L. C. JOHNSTON and R. A. DONALDSON, *Departments of Urology and Radiology, Belfast City Hospital, Belfast*

Case Report

A 64-year-old man had recurring left loin pain for 3 years and had episodes of painless haematuria for 3 months. Cystourethroscopy 4 months before his current admission revealed a normal bladder and an intravenous urogram demonstrated a 1.3 cm calculus in the left renal pelvis and a 0.3 cm stone in the lower pole calix. Immediately before his admission he had heavy painless haematuria for 3 days. He was admitted for a planned left percutaneous nephrolithotomy (PCNL). Examination

revealed slight tenderness in the left loin, routine biochemistry was normal and haemoglobin was 14.5 g/dl.

A single stage PCNL was carried out without difficulty, puncturing the lower pole calix, dilating the track to 30 F and removing the larger stone intact. A tube drain was left through the nephrostomy track. Apart from slightly more haematuria than normal, his post-operative course was uncomplicated. The nephrostomy tube was removed on the fourth post-operative day and he left hospital 7 days after the procedure, with a haemoglobin of 10.4 g/dl.

He was readmitted the following day with pain in the left loin, haematuria and clot retention. An ultrasound scan of the kidney showed clot in the renal pelvis and he was transfused with 2 units of blood. Three days later he had an acute episode of haematuria requiring transfusion of a further 2 units. An arteriogram performed with a view to performing selective embolisation of the source of the bleeding demonstrated early venous filling due to an arteriovenous fistula and a 1.5 cm false aneurysm in the lower pole of the kidney (Fig. 1). Two feeding arteries were embolised with spring coils but the aneurysm continued to fill from an abnormal artery arising at an acute backward angle from the renal artery at the hilum of the kidney (Fig. 2). This angulation made it impossible to position the catheter to enable embolisation of this vessel and the only option was complete embolisation of the renal artery. This was successful and there were no further episodes of bleeding or other complications.

Comment

Excessive bleeding requiring intervention follow-



Fig. 1 Arteriogram demonstrating early venous filling from arteriovenous fistula in lower pole of the kidney.

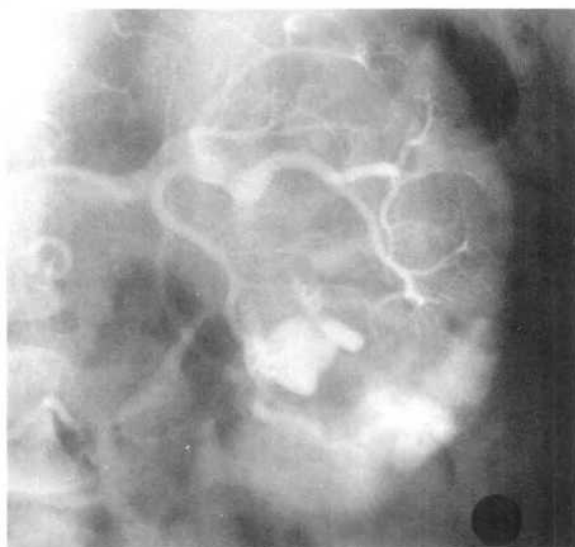


Fig. 2 Pseudoaneurysm filling from aberrant artery despite embolisation of 2 feeding vessels.

ing PCNL occurs in approximately 1 to 3% of cases (Clayman *et al.*, 1984; Patterson *et al.*, 1985) and can usually be successfully controlled by highly selective embolisation of the feeding artery. We are not aware of any reports where an attempt at selective embolisation has resulted in loss of the kidney. Selective embolisation was not successful in this case owing to abnormal arterial anatomy which made it impossible to embolise the feeding artery selectively without embolising the entire kidney. Open surgery may have allowed ligation of the aberrant vessel without sacrificing the kidney.

The possibility of abnormal vascular anatomy should be borne in mind in patients bleeding after PCNL. This is especially important in patients with a single kidney and in these cases, if at arteriography an attempt at selective embolisation is thought to involve risk to the kidney, then consideration should be given to whether open exploration of the kidney would be a safer option.

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Requests for reprints to: R. M. Kernohan, Department of Urology, St Peter's Hospital, Henrietta Street, London WC2E 8NE.

Urachal Cysts in the Bladder Wall

T. HABUCHI and M. MIYAKAWA, *Department of Urology, Shimada Municipal Hospital, Shimada, Shizuoka, Japan*

Case Report

A 44-year-old woman was referred with an abnormal mass in the bladder wall, discovered incidentally during a routine ultrasound examination. She had no history of urinary infection and no urinary symptoms.

Cystoscopy revealed a fingertip-sized round mass protruding into the bladder cavity with normal epithelium posterolateral to the air bubble. CT showed a 2 × 2.5 cm round mass, with rim enhancement by contrast administration, in the right side of the apex of the bladder wall (Fig. 1).

The mass, which was excised during partial cystectomy, was composed of 2 cystic structures; the one on the mucosal side was 1 cm in diameter and the other (on the serous side) was smaller. Histologically, the walls of both cysts were lined by columnar epithelium with several goblet cells and no malignant change. The surrounding connective tissue was severely infiltrated with inflammatory cells (Fig. 2). The diagnosis was urachal cysts in the bladder wall.

Comment

Urachal cysts usually remain clinically silent until infection occurs or they increase in size (Spataro *et al.*, 1983). Most of them develop in the lower third of the urachus and the location of the cysts in our case is unusual (Duckett and Caldamone, 1985).



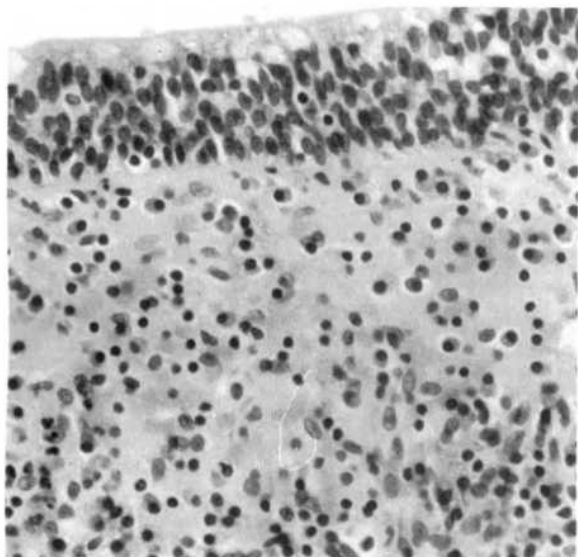


Fig. 2 H and E $\times 200$.

Whether asymptomatic urachal abnormalities, as in our case, need surgical excision remains controversial. Some authors recommend aggressive treatment with wide excision because malignant degeneration of the urachal remnants is possible and cannot be clarified by non-invasive studies (Bourne and May, 1977). However, urachal cysts are very rare and the incidence of occult malignancy is unknown, so that optimal treatment has not yet been established.

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An Unusual Bladder Calculus

T. SARAVANAPAVANANTHAN, *Department of Pharmacology, University of Jaffna, Kokuvil, Sri Lanka*

Case Report

A 28-year-old married male was admitted to the medical ward with recurrent lower urinary tract infection. Radiographic examination revealed a bladder calculus.

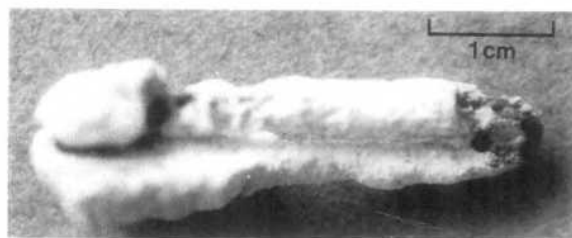


Fig.

The urine was infected and alkaline, which made us suspect a magnesium ammonium phosphate or calcium phosphate stone or a mixture of the two. He was operated on after the infection had been controlled. At operation a bell-shaped vesical calculus (Fig.) was retrieved. On cutting the stone for analysis the nucleus was found to be a closed safety pin $\frac{1}{2}$ cm wide and $3\frac{1}{2}$ cm long. The patient had not had any previous operations. Since he was deaf and dumb he was interrogated with the help of his mother, but he denied self-introduction. However, it was presumed that he had introduced it *per urethram*. The calculus was analysed by the method of Hodgkinson (1971) and was found to be composed of magnesium ammonium phosphate (45 g%) and hydroxy apatite (34 g%).

Acknowledgement

I thank my colleagues for permission to report this case and Drs K. Parthipan, G. Gitanjali and R. Chrishanthi for their technical assistance.

Reference

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Requests for reprints to: T. Saravanapavananthan, Department of Pharmacology, Faculty of Medicine, University of Jaffna, P.O. Box 57, Thirunelvely, Jaffna, Sri Lanka.

Trichouria Due to Benign Retrovesical Teratoma

A. BASU, K. N. CHACKO and A. P. PANDEY, *Department of Urology, Christian Medical College Hospital, Vellore, India*

Case Report

A 10-year-old boy presented with an 8-year history of several episodes of acute urinary retention due to the presence of hairs, requiring urethral catheterisation. He had a palpable urinary bladder and a 3×3 cm mass anterior to the rectum. The urine contained *Klebsiella pneumoniae* sensitive to gentamicin sulphate.

X-ray of the pelvis showed calcified densities overlying

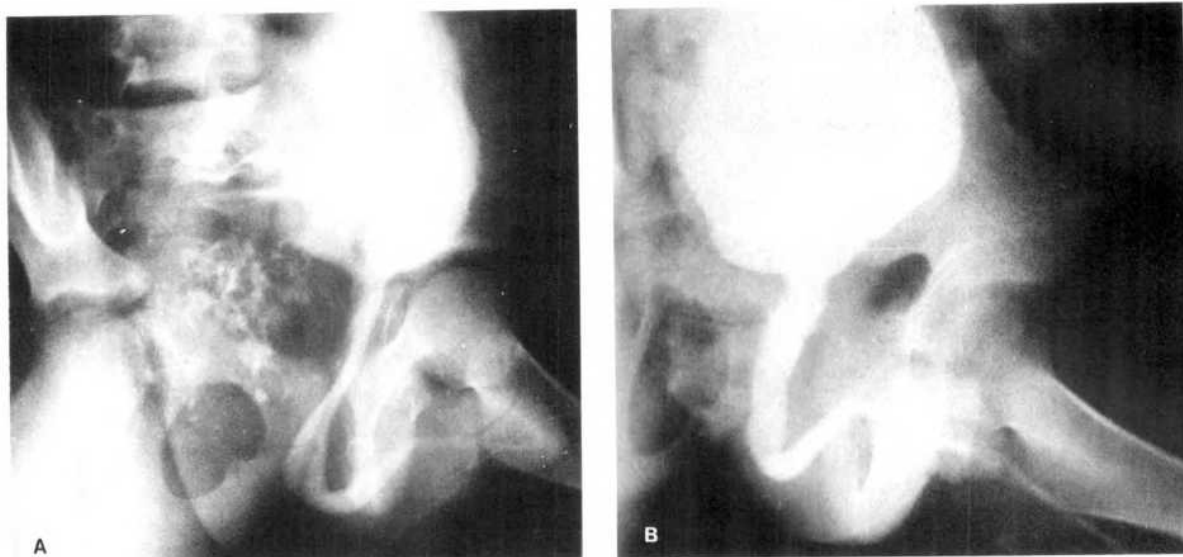


Fig. 1 (A) Pre-operative micturating cystourethrogram. (B) Post-operative micturating cystourethrogram.

the first sacral vertebra on the left side and multiple small calcifications just above the symphysis pubis. Micturating cystourethrography (MCU) revealed compression of the bladder neck and posterior urethra by this calcified mass (Fig. 1A). An IVU showed poor visualisation of the left kidney and hydronephrosis of the right kidney. Cystoscopy revealed hair balls and a large mass at the bladder neck. Biopsies from this mass were reported as benign. On opening the bladder by a midline infra-umbilical incision, a tuft of hair was found entering it from an opening in the posterior wall. A firm, skin-covered mass was felt inside the opening. The bladder was bivalved and this mass was excised, as was another mass lying behind the bladder neck. Post-operative recovery was uneventful. Follow-up MCU (Fig. 1B) was normal and ultrasound revealed a normal right kidney but residual dilatation in the left kidney. Histopathology of the tumour was benign cystic teratoma.

Comments

Presacral tumours are large, present at birth and arise between the rectum and sacrum (Ravitch and Smith, 1951).

The presence of visible soft tissue calcification, the absence of sacrococcygeal defects on radiological examination, the lack of family history and the absence of other congenital anomalies all suggest this was not a case of hereditary presacral teratoma (Hunt *et al.*, 1977). The incidence of malignant change varies from 10 to 50% in various series and is directly related to the age of the patient (Woolley, 1986).

References

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Requests for reprints to: A. P. Pandey, Department of Urology, Christian Medical College Hospital, Vellore—632 004, India.

Notices

British Association of Urological Surgeons

President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting: Scarborough. 10–13 July 1990

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

BAUS Travelling Fellowship

The British Association of Urological Surgeons offers a Travelling Fellowship of £1000.00 for any article(s) of outstanding merit published each year (2 volumes) in the British Journal of Urology. Candidates for the prize must be Fellows of the Royal College of Surgeons in the British Isles, Canada, Australia or South Africa; they must be undergoing urological training or have obtained a consultant post not more than 10 years before the date of submission of the paper. In the case of multiple authorships the authors would have to decide which of them should receive the prize. The successful prize winner must submit a programme of visits to urological centres outside Britain for consideration by the adjudicators, who shall be the President, the Editor of the British Journal of Urology and the Honorary Editorial Secretary. This prize is not necessarily awarded annually.

Norwich Eaton Travelling Scholarship

The scholarship(s) will cover travel, accommodation and registration expenses associated with attending the Society of University Urological Residents and American Urological Association meetings. They will be awarded annually until such time as either the Senior Urological Registrars Group or Norwich Eaton Ltd decide not to continue and will be available to any person appointed to an accredited urological training post.

The scholarship(s) will be awarded to the person(s) presenting the winning paper at the Senior Urological Registrars Group Annual Meeting. The

winning paper(s) will be selected by those members of the Senior Urological Registrars Group present at the meeting and appointed to urological training posts.

Shackman Travelling Fellowship 1991

Applications are invited from Medical Practitioners registered in the United Kingdom who are Senior Registrars in an accredited training programme in urology or Consultant Urological Surgeons of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for applications is 1 September 1990.

Further particulars from and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

C.-E. Alken Prize

An endowment fund has been established to further clinical work and research in the field of Urology by presenting an annual award of SwF 10,000 for outstanding scientific endeavours. The award will be for an unpublished work in the field of Urology. An award certificate will also be presented. The prize money may be divided among several contributors.

The papers may be written in either German or English and three copies must be submitted by 30 September 1990 to: Stiftungsrat C.-E. Alken-Stiftung, Advokaturbüro Dr F. Kellerhals, Bundesplatz 4, CH-3011 Bern, Switzerland.

Each submission must be affixed with a code word and must not bear the author's name. In addition, a sealed envelope labelled with the code word is to be included, containing on a separate sheet of paper the author's name and professional standing, together with the code word.

The adjudicators for the award will be the Board of Directors of the endowment fund and their decision will be final.

Diary

1990

- May 20–24 European Nuclear Medicine Congress 1990. Amsterdam, The Netherlands. Contact QLT/Congrex, Keizersgracht 782, 1017 EC Amsterdam, The Netherlands.
- May 27–June 3 Urological Society of Australasia. 43rd Annual Scientific Meeting Darwin–Kakadu. Contact ASM Secretariat, Urological Society of Australasia, 145 MacQuarie St, Sydney 2000, Australia. Tel: 27 4461
- June 9–10 Société Belge d'Urologie: 55th Congress. Brussels, Belgium. The topic will be "Medical Films on Urology". Contact Dr F. F. Wart, C.H.U.-I.M.C.A.G., Division of Urology, Boulevard Zoe Drion 1, B-6000 Charleroi, Belgium.
- June 12 First Annual Meeting of the European Society of Paediatric Urology. Amsterdam, The Netherlands. The topic will be Posterior Urethral Valves. Contact Dr P. Mouriquand, "Le Dizenier", 11 impasse Mouillard, 69009 Lyon, France.
- June 13–16 Ninth Congress of the European Association of Urology. Amsterdam. Contact QLT Convention Services, Keizersgracht 792, 1017 AC Amsterdam, The Netherlands. Tel: 010 31 20261372
- June 18–22 Revision Course, Diploma in Urology. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
- June 24–28 Canadian Urological Association Meeting, Vancouver, British Columbia, Canada. (To be held jointly with members of BAUS). Contact Dr J. P. Collins, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada.
- June 28–30 Video Urology 90. Second Urological World Meeting based exclusively on videos. La Coruña, Spain. Contact Scientific Secretary, BOK, S.A., C/ Juan Alvarez de Mendizábal, 68, 1.º C, 28008 Madrid, Spain.
- July 10–13 BAUS Annual Meeting, Spa Conference Centre, Scarborough. Contact Secretariat, Royal College of Surgeons, Lincolns Inn Fields, London WC1. Tel: 01 405 1390
- September 9–11 Biannual Conference of International Society for Dynamics of the Upper Urinary Tract. Stockholm, Sweden. Contact Anne-Charlotte Kinn, Department of Urology, St Görans Sjukhus, 112 81 Stockholm, Sweden.
- September 12–15 20th Annual Meeting of the International Continence Society, Aarhus, Denmark. Contact Dr J. P. Norgaard, Institute of Clinical Experimental Research, University of Aarhus, DK-8000 Aarhus C, Denmark
- September 27–28 Fifth Annual Paediatric Urology Course, Cambridge. Places are limited and early application is advisable. Contact Mr R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.
- September 30–October 7 New York Section, American Urological Association Meeting, Budapest. Contact Eva Sloane, New York Section, American Urological Association, 2 East 103rd Street, New York, NY 10029, USA.

- October 1–4 92nd Congress of French Urology. Paris. Contact Convergences, Eurochirurgie—A.F.C. 90, 120 Avenue Gambetta, 75020 Paris, France.
- October 4–5 **Urological Management of Spinal Injury. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.**
- October 16–19 25th Annual Meeting of the Egyptian Urological Association. Cairo, Egypt. Contact Dr Ahmad S. Bedair, 26 Adly Street, Flat 908, Cairo, Egypt.
- October 17–19 Advanced Stone Management Course. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
- October 25–29 Second International Congress on “The Pelvic Floor”—Update Management. Fort de France, Martinique. Contact Bureau Congress: I.F.R.U.G. “The Pelvic Floor”, 2 Square La Fontaine, 2, Paris 75016, France.
- November 8–9 **Renal Failure and Transplantation. Guy’s Hospital, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.**
- November 10 Basic Science and Urology Symposium, Glasgow. Contact Mr R Scott, Department of Urology, Royal Infirmary, 16 Alexandra Parade, Glasgow G31 2ER.
- 1991
- January 22–25 Eighth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev Hospital, Herlev, Denmark. Contact F. Rasmussen, Department of Urology, Herlev Hospital, 2730 Herlev, Denmark.
- February 3–6 International Conference on Orgasm. New Delhi, India. Contact Professor Prakash Kothari, First International Conference on Orgasm, 203 A, Sukhsagar. N. S. Patkar Marg, Bombay 400 007, India.
- September 4–7 Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllői ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016.

Those meetings in heavy print are under the auspices of BAUS.

Addenda

re Ultrasound and plain X-ray screening in childhood urinary tract infection. D. C. Hanbury et al. *Br. J. Urol.*, **64**, 638–640, 1989.

In the Discussion section of the above article it was stated that it was an advantage to 254 of 309 children (91%) that they did not have unnecessary micturating cystography and intravenous urography. The percentage should have been 82% and not 91%. The authors apologise for this error.

re Evaluation of surgical procedures for bilharzial strictures of the ureter. E. M. Awad et al. *Br. J. Urol.*, **64**, 134–137, 1989.

The initials of the first author of the above article should have been R.M. and not E.M. The Journal apologises for this error.

Book Reviews

Current Perspectives in Paediatric Urology (Clinical Practice in Urology Series). Edited by R. H. Whitaker. Pp. xi+124. London, Berlin, Heidelberg, New York, Paris, Tokyo, Hong Kong: Springer-Verlag. 1989. Price: £49.50.

This book is based upon lectures given by paediatric urologists during the annual two-day paediatric urology course organised by the Editor in Cambridge. The topics are wide ranging and were chosen either because they are controversial or because they are difficult to understand. The book does not set out to be a comprehensive textbook of paediatric urology.

The chapters vary from a superficial overview, *e.g.* renal duplication and intersex, to an in-depth analysis of a limited topic, *e.g.* pelviureteric junction obstruction in the neonate. The text is easy to read but extremely annoying because of the lax English. Phrases like "... poor bit of developing kidney" abound. It reads as though the text had been transcribed straight from a tape recording of the lectures rather than written by the contributors.

In spite of these criticisms this book will be useful for those Senior Registrars requiring last-minute revision for the third examination. At £49.50, however, many may well think that it is too expensive.

Manual of Clinical Problems in Urology. Edited by M. I. Resnick and M. A. Benson. Pp. xi+286. Boston, Toronto, London: Little, Brown and Company. 1989. Price: £9.95.

This American textbook was written for the medical student or houseman and as such misses that objective. The book contains an enormous amount of clinical material, made possible by the small, closely packed print which in itself makes it difficult to read. In this type of book, where an attempt is made to cover most subjects, the balance is important and again this is not achieved. In clinical practice, bladder carcinoma and its management are very common; bladder transitional cell tumour is covered but no comment is made on chemotherapy or radiotherapy. In contrast, 5 pages are devoted to megaloureter.

These comments aside, the text is well written and there are short bibliographies at the end of each subsection directing the reader to more comprehensive texts and reviews. At just under £10 this book is worth purchasing and it fits into the white coat pocket, making it easily accessible to the urological trainee.

The Causation and Clinical Management of Pelvic Radiation Disease. Edited by P. F. Schofield and E. W. Lupton. Pp. xviii+153. London, Berlin, Heidelberg, New York, Paris, Tokyo, Hong Kong: Springer-Verlag. 1989. Price: £49.50.

Radiotherapy has had an integral role in the curative treatment of pelvic malignancy for many years. The number of patients receiving radiotherapy as part of their management has increased in recent years and is likely to continue to increase in the future.

The potential side effects of such treatment are well known to clinicians involved in the care of these patients and it is generally accepted that a proportion of patients will have troublesome side effects as part of the trade-off against cure. It is, therefore, timely to have a very readable book dedicated solely to the diagnosis and management of radiation disease in the pelvis.

The book does not cover radiotherapeutic aspects in detail and there is no attempt to relate radiotherapy techniques to subsequent damage. The book concentrates on the investigational techniques available and the treatment of severe late effects.

This is a very useful text for all those who are involved in the treatment and subsequent care of patients with pelvic malignancy. Although of particular relevance to surgeons involved with the treatment of radiation-induced injury, this is certainly of interest to all radiotherapists.

Incontinence. By R. C. L. Feneley, J. G. Malone Lee and S. L. R. Stanton. Pp. 48. London: British Medical Association. 1989. Price: £1.20.

This small pocket book for sufferers of incontinence is of the type that one wishes were available to cover most of the clinical conditions with which we deal. It provides thorough, though simple, explanations of normal function, what goes wrong and what we usually do about it, without being at all patronising in style.

At only £1.20 it is an information resource for patients which incontinence clinics may feel able either to fund themselves or to offer for sale to their patients, and the book is recommended as such.

Urology Annual 1990. Volume 4. Series Editor: S. N. Rous. Pp. xi+300. East Norwalk: Appleton and Lange. 1990. Price: £54.35.

The fourth volume of this series continues to identify many of the main contemporary issues in urology. Topics that perplex the urologist are well presented and discussed by acknowledged experts. Thus—AIDS and the urologist, ultrasound in the diagnosis of carcinoma of the prostate,

flow cytometry and bladder cancer, carcinoma *in situ* of the bladder, immunotherapy, MRI in urology, coumarin for renal carcinoma and a review of the current technology of ESWL—all attracted the attention of this reviewer.

Once again the purpose of this series has been admirably achieved but it is inevitable that there are points of disagreement and some disappointments. The issues on AIDS are well summarised but the authors fail to emphasise the enormous difference between elective surgery and emergency surgery both in the risks and attitudes by surgeons; risks of contamination may be very low but the risk of contamination from an unconscious, high risk patient does create a difficult situation

with regard to consent and blood testing for AIDS. The review on carcinoma *in situ* in the bladder highlights the alternatives in therapy but emphasises firmly that radical surgery must not be delayed when intravesical treatment has failed to achieve a response. There is no real attempt to distinguish between the different groups of carcinoma *in situ* (primary, with superficial transitional cell carcinoma, with invasive transitional cell carcinoma and involving prostatic ducts/stroma): this is an important aspect of the subject and deserves some elaboration to help the reader.

This book is full of up-to-date material on many important subjects and deserves a place in every urological department.

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